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Control of carbapenemase-producing Enterobacteriaceae outbreaks in acute settings: An evidence review

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Running head

Control of CPE outbreaks in acute settings: an evidence review

Abstract

Background

In recent years infections with carbapenemase-producing Enterobacteriaceae (CPE) have been increasing globally and present a major public health challenge.

Aim

To review the international literature to: i) describe CPE outbreaks in acute hospital settings globally, and ii) identify the control measures used during these outbreaks and report on their effectiveness.

Methods

We systematically searched MEDLINE and EMBASE databases, abstract lists for key conferences, reference lists of key reviews, and sought information on unpublished outbreaks, for 2000-2015. Where relevant, risk of bias was assessed using the Newcastle-Ottawa scale. We conducted a narrative synthesis of the evidence.

Findings

Ninety-eight outbreaks were eligible. These occurred worldwide, with 53 reports from Europe. The number of cases (CPE infection or colonization) involved in outbreaks varied widely, from 2-803. In the vast majority of outbreaks multi-component infection control measures were used, commonly including: patient screening, contact precautions (e.g. gowns, gloves), handwashing interventions, staff education or monitoring, enhanced environmental cleaning/decontamination, cohorting of patients and/or staff, and patient isolation. Seven studies were identified as providing the best available evidence on the effectiveness of control measures. These demonstrated that CPE outbreaks can be successfully controlled using a range of appropriate, commonly used, infection control measures. However, risk of bias was considered relatively high for these studies.

Conclusion

Our findings indicate that CPE outbreaks can be controlled using combinations of existing measures. However, the quality of the evidence-base is weak and further high-quality research is needed, particularly on the effectiveness of individual infection control measures.

Key words

Carbapenemase-producing Enterobacteriaceae; Carbapenem-resistant Enterobacteriaceae; acute settings; outbreak; infection control

Introduction

In recent years infections with carbapenemase-producing Enterobacteriaceae (CPE) have been increasing globally[1-3]. Carbapenem antibiotics are usually reserved for treating serious drug resistant infections[4], thus the emergence of resistance to this class of antibiotics is a major public health concern. Patients infected with CPE have limited treatment options, and high mortality rates (26%–44%, based on a recently published review)[5]. CPE transmission may occur in both healthcare and community settings[1, 6, 7]. Hospitalized patients may be particularly susceptible to infections; CPE is associated with increased risks of morbidity and mortality, prolonged hospital stays, and increased healthcare costs[8, 9]. A number of risk factors for CPE acquisition have been identified, including previous hospitalization (particularly abroad e.g. in an endemic country), prolonged hospitalization, previous exposure to antibiotics, surgery, organ or stem-cell transplantation, critical illness / residency in an intensive care unit, transfer between units, and exposure to invasive/indwelling devices (e.g. catheters)[8, 10-14]. Outbreaks associated with contaminated endoscopic equipment have also been documented[15-18].

The control of CPE in hospital settings is not only costly[19] but presents a significant challenge. Reliable laboratory detection of CPE is an essential first step but may be hampered since a range of different mechanisms can cause resistance, and this may occur to varying degrees; not all laboratories are equipped to detect all types of CPE[20-22]. Meanwhile, asymptomatic CPE-colonized patients may be an important source of infection, spreading the bacteria to other patients before they are identified as carriers[22]. These difficulties in the detection of cases, combined with the challenges in treating the infection once it is diagnosed, may allow for the rapid dissemination of CPE. Various agencies, societies and countries have developed guidelines on CPE control[23]. These recommend a range of control measures including early detection of cases, isolation of patients, patient/staff cohorting, and enhanced hygiene measures[24]. However, evidence on the effectiveness of such measures is lacking, as highlighted in a review of measures to prevent the transmission of CPE through cross-border transfer of patients conducted by the European Centres for Disease Control (ECDC)[25].

CPE outbreaks occur in acute settings with worrying frequency and there is a need to identify the most effective methods of controlling these. We therefore conducted a comprehensive evidence review with two main objectives: i) to describe CPE outbreaks in acute hospital settings globally, and ii) to identify the control measures used during these outbreaks and report on their effectiveness.

Methods

Study conduct

Our review was conducted based on the Cochrane Handbook for Systematic Reviews of Interventions[26], and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[27].

Search strategy

We carried out electronic database searches in MEDLINE and EMBASE for papers published in the English language during 2000-2015 on 5th May 2015. Searches combined MeSH terms and free-text key words. Search terms for ‘CPE’ were based on the those used in the ECDC review[25]. We also searched the Cochrane Library together with reference lists of relevant reviews. Abstract lists for conferences of the following organisations were searched: Public Health England (PHE), the

Healthcare Infection Society (HIS) and Infection Prevention Society (IPS), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the Centres for Disease Control and Prevention Epidemic Intelligence Service (EIS), and the Federation of Infection Societies (FIS). To obtain information on unpublished outbreaks we searched the Public Health England outbreaks database and also requested information on European outbreaks via the ECDC. We imported all records into an Endnote database.

Study selection

To be eligible for inclusion in the review as a whole, studies had to: i) report on a CPE outbreak in an acute setting, and ii) report on the control measures used during the outbreak. Once the final list of eligible studies had been selected, we identified a sub-set of studies providing the best available evidence on the effectiveness of control measures. The PICO for the sub-study was Patients: patients in an acute care setting at potential risk of CPE infection or colonisation in the context of an outbreak, Intervention: introduction of (any type of) specific infection control measures, Comparator: no introduction of these specific infection control measures (or introduction of less rigorous measures), Outcome: measure of the occurrence of CPE colonisations and/or infections (e.g. number, rate). To be eligible for inclusion in the sub-set, studies had to: a) utilize a comparator group (e.g. phased introduction of control measures enabling comparisons), b) provide sufficient detail on the type and timing of infection control measures, and c) quantitatively report on the outcome in the intervention and comparator groups.

For the purpose of this review, an outbreak was defined as two or more cases of CPE infection epidemiologically linked in time and place. However, once this definition had been met, to assist in differentiating between an outbreak and prevalence data, if the authors described the situation as an outbreak or cluster then this was accepted. Studies reporting on CPE infections and/or colonisations were eligible, and no restriction was placed on the type of infection control measures used. In selecting studies for inclusion in the review as a whole we included all types of primary studies (e.g. descriptive studies, cohort studies, and trials). Literature reviews, expert opinion and guidance documents were not eligible for inclusion but the reference lists were used to identify any additional eligible primary studies. Although conference abstracts were eligible for inclusion in the review as a whole, they were not considered for inclusion in the sub-set of 'best available evidence' studies due to limited information.

Records were independently screened for eligibility by two reviewers with disagreements resolved by discussion. Where multiple studies on the same outbreak were identified the most relevant with respect to the objectives of the review was selected, and supplemented with additional information from related reports.

Data extraction and definitions

Key data items on infection control measures used and the effectiveness of these were extracted independently by two reviewers. Other basic data items (e.g. country, hospital setting) were extracted by one reviewer - 10% of studies were extracted in duplicate and there were no important differences in data extracted by different reviewers. The following data items were extracted: lead author and study publication date, year in which the outbreak occurred, country, type of hospital setting, brief description of the outbreak (e.g. CPE type, source of outbreak, number of cases), description of the outbreak control measures implemented, any quantitative or qualitative data on the effectiveness of the outbreak control measures, authors conclusions in relation to the effectiveness of control measures. Multi-component interventions were defined as those utilising two or more infection control measures. The term 'contact precautions' (or 'contact isolation precautions') was assumed to include some kind of barrier infection control measure such as the use of gloves/gowns even if not specifically described. Physical isolation of patients (e.g. in single rooms) was not assumed unless explicitly stated.

Data synthesis

Data were narratively synthesized as recommended by the University of York Centre for Reviews and Dissemination[28]. The vast majority of studies were not designed to assess the effectiveness of infection control measures. This, combined with notable heterogeneity between studies, including the range of different control measures applied with most studies implementing multi-component measures, meant it was not appropriate to conduct a meta-analysis.

Risk of bias assessments

Risk of bias was assessed for the sub-set of studies providing the best available evidence on the effectiveness of control measures using the Newcastle-Ottawa scale (NOS)[29]. The NOS assesses bias in observational studies related to selection of participants [four items], comparability [one item] and outcome [three items]. A study can be awarded a maximum of one star for each item within the selection and outcome categories and a maximum of two stars for comparability. Each study was independently assessed by two reviewers with disagreements resolved by discussion.

Results

Included studies

The MEDLINE and EMBASE searches returned 1520 records, with a further 13 identified through other sources (e.g. hand-searches of abstract lists for relevant conferences); 98 outbreaks were eligible for inclusion (Figure 1). Most records were simply outbreak reports describing an outbreak and the infection control measures used, with limited information on the extent to which the outbreak was controlled.

Description of CPE outbreaks (Table I)

CPE outbreaks occurred worldwide, with 53 reports from Europe, 20 from US/Canada, and 9 from Israel. Others were from a wide range of countries including Uruguay, Saudi Arabia, Brazil, China and India. *Klebsiella pneumoniae* was the most common organism, being documented as the sole or one of the main carbapenem-resistant bacteria present in >80% of outbreaks. A wide range of types of outbreaks were apparent, from those affecting a single hospital unit over a period of a few weeks, to hospital-wide outbreaks (in some cases affecting more than one hospital) over a period of several years. Therefore, the number of cases (CPE infection or colonization) involved in outbreaks varied widely, from 2 to 803. Denominators (e.g. number of patients potentially at risk of infection) were often not documented and it was therefore not possible to compare attack rates across outbreaks.

The likely source of the outbreak was not always stated, but where it was documented it was due to an index patient with a history of hospitalization abroad in ten outbreaks, a contaminated hospital instrument (e.g. duodenoscope) in seven outbreaks, and an environmental reservoir (e.g. hospital sink) in four. However, in the majority of outbreaks the source either did not fall into any of these categories or was not specified (e.g. the index patient may potentially have been infected during a previous hospitalization, in a nursing home or in the community) (n=77).

Measures to control CPE outbreaks (Table II)

In the vast majority of outbreaks multi-component infection control measures were used. Standard procedures were often reviewed and reinforced as an initial step. Patient screening (e.g. all patients on the ward, new admissions) was used in 85 of the 98 (87%) outbreaks, use of contact precautions (e.g.

gowns, gloves) in 78 (80%) outbreaks, handwashing interventions (e.g. encouraged or monitored) in 61 (62%) outbreaks, staff education or monitoring of compliance with interventions in 57 (58%) outbreaks, enhanced environmental cleaning/decontamination in 56 (57%) outbreaks (22 of which provided details e.g. chemicals used – see Table II), cohorting of patients and/or staff in 52 (53%) outbreaks, and patient isolation (e.g. isolation of infected or colonized patients in single rooms) in 51 (52%) outbreaks. Less commonly used measures were 'other' screening (e.g. environmental) which was used in 35 (36%) outbreaks, antimicrobial stewardship/ restriction of carbapenem - used in 18 outbreaks, and closure of the ward or unit to new admissions – used in 13 outbreaks (although in some additional outbreaks temporary restrictions were placed on new admissions).

Overall, the majority (n=73, (75%)) of these outbreaks were deemed to have been controlled, though the time taken to bring them under control varied widely, from a matter of weeks/months to years. In nine outbreaks the control measures were deemed insufficient at the time the report was prepared/published (e.g. new cases were continuing to occur), and for the remaining 16 outbreaks the effectiveness of control measures was unclear (e.g. it was not clearly reported by the authors or in some cases CPE became endemic in the setting even if measures helped control the outbreak). The timing of outbreak control measures was often not clearly documented.

Focusing on outbreaks associated with contaminated hospital instruments (n=7), all but one of these were due to contaminated endoscopic equipment[15, 17, 18, 30-33]. In the Carbonne *et al* 2010[18] report the index patient had been previously hospitalized abroad but seven of the secondary cases were associated with a contaminated duodenoscope used to examine the source case. In the remaining study the source was a contaminated pre-operative shaving razor[34]. All outbreaks, except one where no information was provided[33], were successfully controlled. Generally a range of infection control measures were used including review/revision of duodenoscope reprocessing/disinfection procedures.

Meanwhile, of the four outbreaks likely due to an environmental reservoir, this was a sink/sink drain in three[35-37], and a contaminated hospital mattress in one[38]. The latter outbreak was resolved by discarding the contaminated mattress. However, eradicating CPE from sink drains tended to be problematic. Leitner *et al*[36] reported a prolonged outbreak (~2 years) though it was eventually controlled by reinforcing existing infection control measures and replacing all contaminated sinks. Vergara-Lopez *et al*[37] also documented a prolonged outbreak (>2 years). The contaminated sink was removed but this did not fully stop the occurrence of new cases. The elimination of the horizontal drainage system finally eradicated the outbreak. Meanwhile, Kotsanas *et al*[35] reported that attempts at sink sterilisation were futile, and the authors suggest that sink removal and replacement with appropriately designed sinks may be required.

Effectiveness of infection control measures during CPE outbreaks

Seven studies were identified as providing the best available evidence on the effectiveness of control measures[39-45]. Overall, risk of bias was considered relatively high for this sub-set of studies (Table III). However, the seven studies tended to score reasonably highly on the selection of the study population with four studies[39, 40, 42, 44] awarded three stars since the 'exposed' and 'unexposed' cohorts were sufficiently representative and the ascertainment of the exposure (i.e. to infection control interventions) was adequate. Three studies[41, 43, 45] were awarded the maximum possible four stars because patients were screened for CPE on hospital admission in both the intervention and comparator periods thus demonstrating that the outcome of interest was not present at start of study. None of the studies reported the matching of exposed and non-exposed individuals in the study design or adjusting for confounders in the analysis, thus all studies were awarded zero stars for comparability. With regard to the assessment of the outcome, all seven studies[39-45] were awarded two stars (out of a maximum of three); one star because CPE was laboratory confirmed, and one because follow-up was deemed

sufficiently long for the outcome to occur. Adequacy of follow-up of cohorts was, however, insufficient in all studies.

The seven studies are summarised in Table IV. Enfield *et al*[44] conducted a before-after intervention study with an interrupted time series analysis. They implemented a bundled intervention which included staff education, improved hand hygiene, strict isolation, thorough environmental hygiene and assessment, and antibiotic stewardship. A reduction in CPE incidence was reported; from 7.77 cases per 1,000 patient-days in the 12 months prior to the intervention to 1.22 cases per 1,000 patient-days afterwards (p<0.001), though CPE was not completely eliminated. Munoz-Price *et al*[45] report a quasi-experimental study in which a bundle of interventions was applied involving daily 2% chlorhexidine gluconate baths for patients, enhanced environmental cleaning, surveillance cultures at admission, serial point prevalence surveillance, isolation precautions, and staff training. There was evidence of a reduction in prevalence of colonization with KPC-producing isolates from 21% prior to the intervention to 0% at the end of the follow-up period (p<0.001).

In another quasi-experimental study, Ben-David *et al*[39] introduced an enhanced national infection control program in which the key measures were active CPE surveillance and contact precautions for all colonized or infected patients. The authors reported a reduction in the incidence of carbapenem-resistant *K. pneumoniae* from 6.93 cases per 10,000 patient-days during the last quarter of the pre-intervention period to 1.8 cases per 10,000 patient-days during the last quarter of the intervention period, a 4.7-fold decrease (p<0.001). Borer *et al*[40] conducted a quasi-experimental before-and-after interrupted time-series study. The intervention had five key elements: an emergency department flagging system, the building of a cohort ward, the eradication of clusters, environmental and personnel hand cultures, and a carbapenem-restriction policy. There was an observed decrease in the incidence density of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections from 5.26 per 10,000 patient-days in the pre-intervention period to 0.18 per 10,000 patient-days by the end of the intervention period (p<0.001).

Chitnis *et al*[41] utilized a stepwise introduction of infection control measures and used the first stage of the intervention (contact precautions, active surveillance, staff education and audits) as the comparator. Subsequent interventions involved isolation and cohorting of CPE patients with dedicated nursing staff and medical equipment. During the study period, CPE prevalence decreased from 49% to 8% and the percentage of patients screened with newly detected CPE from 44% to 0%, both of which were statistically significant. Ciobotaro *et al*[42] conducted a quasi-experimental study in which the intervention included guidelines for patient isolation, cohorting, and environment cleaning; education of staff; and a computerized notification system for flagging CRKP carriers. Poisson segmented regression demonstrated a significant difference in slope before and after the intervention (p<0.001). The slope showed that during each month after the intervention, the number of CRKP cases decreased by a factor of 0.91 (95% CI: 0.85-0.97) compared with the previous month. Finally, Cohen *et al*[43] introduced their intervention in consecutive steps and reported that only the cohorting of patients and staff (affected patients were admitted to separate areas with dedicated nursing staff and separate medical equipment) was associated with a significant change in both the incidence and prevalence of CPE (both p<0.00; see Table 4 for slope coefficients associated with each of the four intervention periods).

Discussion

Key findings

This review demonstrates that CPE outbreaks are common and have global impact. Indeed, there is growing international concern around the spread of CPE[46, 47]. Outbreaks were documented in a wide range of hospital settings and although many occurred on high-dependency wards (e.g. intensive care

units) this was certainly not always the case. Indeed, quite a number were hospital-wide outbreaks. Awareness of the risk of CPE throughout acute care settings is therefore important.

In the majority of outbreaks the source of CPE was unclear or not specified. Seven outbreaks were associated with a contaminated hospital instrument (mainly duodenoscopes); there is growing interest and concern around such outbreaks[48, 49], highlighting the need for thorough reprocessing procedures. Meanwhile, although there were only four outbreaks where the source was found to be an environmental reservoir, it is of note that 'other screening' (which included environmental sampling, staff screening etc.) was reported to have been conducted in less than a third of outbreaks. It is therefore possible that environmental reservoirs are an under-estimated source of CPE outbreaks, particularly those that are prolonged. Infection control practitioners dealing with CPE outbreaks should therefore consider whether environmental contamination may play a role. This review highlighted that the decontamination of environmental reservoirs such as sink drains is problematic.

Almost all studies in this review used multi-component infection control measures. That the majority of outbreaks were reported to have been ultimately controlled is encouraging and suggests that the control measures currently in use can be effective. However, high-quality evidence was lacking and we only identified seven studies[39-45] meeting our criteria as providing the 'best available' evidence. This limited evidence supports the use of multi-component measures but it is difficult to disaggregate the effectiveness of individual components, or which components are best used together.

All seven studies reported utilising some kind of active surveillance (e.g. screening all patients on admission to a ward, and/or all patients on the ward). It is logical that the early detection of cases may be crucial to prevent spread to other patients. There was also evidence suggesting a beneficial effect of patient and/or staff cohorting (all seven studies), contact precautions (e.g. gloves) (all seven studies), staff education/ensuring optimal compliance[40-45], enhanced environmental cleaning/decontamination[40-45], patient isolation[40, 43, 45], and handwashing interventions[40, 41, 43, 44]. It is interesting that only three of the seven studies reported using antimicrobial stewardship[40, 42, 44] since this may play an important role in preventing future outbreaks of drug-resistant infections (not only CPE)[50-52]. None of the seven studies reported closure of the ward/unit/hospital to new admissions, which may perhaps be considered a 'last resort'. Our findings tie in with those of previous evidence reviews on this topic (neither of which were restricted to outbreaks)[25, 53], and all the aforementioned infection control measures are recommended in current guidelines for the control of CPE and other multi-drug resistant gram-negative bacteria[54-57].

The compliance of hospital staff with infection control measures (e.g. use of gowns/gloves, hand hygiene) may impact on effectiveness. Indeed, the contaminated hands of healthcare staff likely play a key role in the transmission of gram-negative bacteria[58, 59], emphasizing the importance of ensuring optimal compliance. Although all but one of the seven studies (Ben-David *et al* 2010[39]) reported attempts to enhance staff knowledge/compliance with infection control measures, few reported on levels of compliance. Chitnis *et al*[41] documented notable lapses in compliance with hand washing precautions which was performed at less than a third of opportunities, though compliance was higher for gloves (77%) and gowns (89%). Additionally, Munoz-Price *et al*[45] noted that their experience suggested failure to comply with "isolation precautions" was common. An international review of the compliance of healthcare staff with infection control interventions found this to be sub-optimal but also highlighted that structured interventions can improve compliance[60].

Limitations

This review did not aim to capture all CPE outbreaks (only those that provided information on the control measures used). Therefore, it should not be considered to provide an exhaustive list of all CPE outbreaks in acute settings. The reported size of CPE outbreaks varied widely. However, this is likely to depend not only on the severity of the outbreak but also on other factors such as the period of

observation, the extent of screening for CPE, and whether only infected patients were considered or those that were colonised too.

Assessing the effectiveness of CPE infection control measures, particularly in the context of an outbreak, is subject to some important limitations. Due to the difficulty in detecting CPE in the laboratory, under-ascertainment of cases may be an issue during outbreaks. Diagnostic methods for the detection of Carbapenem resistance organisms have been evolving, traditional culture based methods may be used and molecular methods have also been developed to identify resistance mechanisms, however, no single method can detect all carbapenem resistance mechanisms[61].This may hinder the early recognition of cases and thus the timely initiation of infection control measures (e.g. isolation or cohorting of affected patients). The vast majority of reports included in the review as a whole were simply outbreak reports and not specifically designed to assess effectiveness of infection control measures. As expected, we did not identify any eligible randomized controlled trials. Observational studies may be subject to many biases that are difficult to avoid. Indeed, the risk of bias in the seven studies providing the best available evidence on the effectiveness of control measures was judged as relatively high overall. The findings of these studies should therefore be interpreted with some caution.

There was a lack of clarity around reporting of control measures. The ORION statement (guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection) recommends avoiding the use of terms such “contact or strict isolation, barrier nursing, enteric or skin precautions” to describe isolation interventions, as these may not have universal meaning[62]. Such generic terms were frequently used in the outbreak reports included in this review. Furthermore, in some reports control measures were mentioned very briefly (e.g.”measures included x y z”) and we therefore can’t be sure that all measures used were actually documented. In many cases the ‘standard’ infection control measures (i.e. those in place prior to the outbreak) are not adequately described.

Publication bias may also be an issue. For example, outbreaks that have not been successfully controlled may be under-reported in the published literature. However, this is more likely to be a concern with regard to general outbreak reports rather than the sub-set of studies specifically designed to assess the effectiveness of control measures. We sought information on unpublished outbreaks in order to help minimise this potential source of bias; however of those we found none met the eligibility criteria for inclusion.

Conclusions

CPE is an ongoing and challenging global public health problem. Outbreaks provide an opportunity to evaluate control measures to inform future guidelines. Better reporting of CPE outbreaks, in line with the ORION statement[62] would be helpful. Though many reported CPE outbreaks appear to be successfully controlled, optimising the timeliness of control measures and better understanding of which control measures are most effective will enable resources to be most wisely allocated and reduce transmission. Environmental transmission may play an important part in hospital outbreaks and it should be considered. There is an urgent need for further high quality studies to evaluate measures to control CPE outbreaks ideally using a staggered approach to the introduction of interventions.

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Table I. Details of CPE outbreaks (ordered by geographic area)

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
Leitner, 2014[36]	2011-2013	Austria	Haematology Ward	KPC-2-Producing *Klebsiella oxytoca*	The index patient was in the medical ICU in December 2010. The patient was colonized, not infected. The patient was then transferred to the haematology ward, where contact precautions were continued. KPC-producing *K. oxytoca* isolates with resistance patterns identical to those of the outbreak strain were identified from 10 more patients in the Haematology unit. Three patients were identified in late 2011 and 2012, and seven were detected from January to July 2013. Six patients developed an infection. Investigations revealed carbapenamase resistant *K. oxytoca* isolates in sink drains.	Environmental reservoir
Novak, 2014[63]	2012	Croatia	Intensive care unit	VIM-1-carbapenemase-producing *Enterobacter cloacae*	In the period between June and August 2012, five patients were infected and one patient colonised with MDR VIM-1-producing *E.cloacae*. Among all patients admitted to the ICU only this one patient was colonised after 21 days of hospitalisation, without developing clinical infection. Four of the five infected patients died.	Other or not known
Kanerva, 2014[64]	2013	Finland	A ward in a long-term acute care hospital	Carbapenemase-producing *Klebsiella pneumoniae* (KPC)	The index case detected by routine clinical culture in June 2013. The first screening revealed four KPC-carriers in a 5-bed room and the following rounds four KPC-carriers one at a time. None of the other exposed patients were positive. None of the KPC carriers developed clinical infection within a 6-month follow-up.	Other or not known
Carbonne, 2010[18]	2009	France	Several hospitals	KPC-2-producing *Klebsiella pneumoniae*	In September/ October 2009 there were 13 cases in total (four with infections and nine with digestive tract colonisations), including a source case transferred from a Greek hospital. Seven were secondary cases associated with use of a contaminated duodenoscope used to examine the source case and five were secondary cases associated with patient-to-patient transmission in hospital.	Index patient and contaminated hospital instrument
Cuzon, 2011[65]	2010	France	Intensive care and internal medicine unit	OXA-48 *Klebsiella pneumoniae*	Seventeen *Klebsiella pneumoniae* isolates producing the OXA-48 carbapenemase, obtained from 10 patients hospitalized from April to June 2010, mostly in the medical intensive care unit, were analyzed. Seven	Other or not known

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
					patients were infected.	
Kassis-Chikhani, 2010[66]	2003-2004	France	Liver transplant centre	Imipenem-resistant VIM-1-producing *Klebsiella pneumoniae*	Following admission of index case on 2 December 2003 (transferred from Greece), seven secondary cases ensued.	Index patient with history of hospitalisation abroad
Levast, 2011[67]	2011	France	Not specified - assume obstetric unit	OXA-48-positive carbapenem-resistant *Klebsiella pneumoniae*	The first case was a pregnant woman who had returned from Turkey. Screening of patients (infants and mothers) hospitalized in the same unit once a week during the following 3 weeks identified a neonate as a carrier of a *K. pneumoniae* isolate that exhibited a similar pattern of resistance.	Index patient with history of hospitalisation abroad
Semin-Pelletier, 2015[68]	2013-2014	France	Hospital-wide	OXA-48 producing *Klebsiella pneumoniae* and *Citrobacter freundii*	The outbreak period began on 2 May 2013, the admission day of the index case, and ended in August 2014 with 72 secondary cases in three departments.	Other or not known
Ducomble, 2015[69]	2010-2012	Germany	Tertiary care hospital	KPC-2-producing *Klebsiella pneumoniae*	The index case was a patient transferred from a Greek hospital in June 2010, from whom an isolate with KPC-2-producing *K. pneumoniae* was recovered 10 days later. By 31st July 2012, 71 further cases (around half were infected and half colonised) had been detected.	Other or not known
Kola, 2015[15]	2012-2013	Germany	Hospital-wide, mainly intensive care unit	OXA-48 *Klebsiella pneumoniae*	Between December 6, 2012 and January 10, 2013, carbapenem-resistant *K. pneumoniae* (CRKP) was cultured from 12 patients staying on 4 different wards. There was a spatial relationship between 6 of the cases which were located on the same wards. The remaining 6 cases were all related to endoscopic retrograde cholangiopancreatography (ERCP) which was performed with the same duodenoscope.	Contaminated hospital instrument
Lubbert, 2013[70]	2010-2013	Germany	Intensive care unit (not completely clear whether all cases occurred in	KPC-2-producing *Klebsiella pneumoniae*	After the index case was detected in July 2010, a large outbreak evolved with 103 cases became either colonised (n=60) or infected (n=43) through to April 2013.	Index patient with history of hospitalisation abroad

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
			this unit though)			
Steinmann, 2011[71]	2010-2011	Germany	Intensive care unit	*Klebsiella pneumoniae* harbouring KPC-2 and VIM-1	Seven patients were involved in the outbreak. The first had CRKP was isolated from their blood. Two weeks later two further patients (who were not in the same ICU room), were found to have invasive infections with this strain. During the next 12 days three further patients tested positive for this strain, two of whom were colonized only (rectally).	Other or not known
Wendt, 2010[58]	2008	Germany	Surgical intensive care unit	KPC-producing *Klebsiella pneumoniae*	In January 2008, a *K.pneumoniae* was isolated from the index patient who was nursed on the interdisciplinary ICU. A KPC-2 was identified after *K. pneumoniae* with identical susceptibility patterns had been isolated from two more patients. Despite the introduction of infection control measures, transmission occurred in five additional patients and three of the patients died from infections.	Other or not known
Douka, 2015[72]	2011	Greece	Intensive care unit	Pandrug-resistant VIM-1-producing *Providencia stuartii* clonal strain	The first PDR *P. stuartii* strain was isolated on 2 September 2011 from a 74-year-old male patient (index case) admitted to the ICU2 17 days previously. Soon afterwards, other cases occurred in the same ICU (10 patients, including the index case), in the ICU1 (three patients) and in the intermediate care unit (two patients). All PDR *P.stuartii* isolates were recovered from cultures ordered by the attending physician in the presence of signs and symptoms of infection (no surveillance cultures were performed during that time period).	Other or not known
Karampatakis, 2012[73]	2011	Greece	Internal medicine, surgical units and ICU	Carbapenemase-producing *Klebsiella pneumoniae* and *Enterobacter cloacae*	The outbreak began on February 2011 with four cases and reached the maximum on July 2011 with 21 cases.	Other or not known
Papadomichelakis, 2009[74]	2007-2009	Greece	Intensive care unit	KPC-producing *Klebsiella pneumoniae*	The outbreak was first noticed in late September 2008 and all patients found to be colonised or infected with KPC-Kp from January 2007 to March 2009 were included in the study. From August 2007 to March 2009, KPC-Kp was isolated from 53 patients.	Other or not known

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
Souli, 2010[75]	2007-2008	Greece	Intensive care unit	Carbepenemase 2 (KPC-2) -producing *K.pneumoniae*	From January 2007 through December 2008, 50 patients (34 in the ICU were colonized (n=32) or infected (n=18))	Other or not known
Voulgari, 2014[76]	2011-2013	Greece	Hospital-wide	NDM-1-producing *Klebsiella pneumoniae*	In total 78 NDM-1-producing K. pneumoniae, which were harvested from 71 patients and were implicated in two distinct outbreaks. The first extended from November 2011 to December 2011 and involved four patients in the haematology department. The second occurred between May 2012 and June 2013 and was ongoing [at the time of writing] with a total of 67 patients involved, from whom 74 NDM-producing *K. pneumoniae* were harvested.	Other or not known
Voulgari, 2013[77]	2011-2012	Greece	Hospital-wide	OXA-48-producing *Klebsiella pneumoniae*	From December 2011 to March 2012, 13 *K.pneumoniae* isolates were recovered from nine patients. Index isolate K1 was retrieved from a female patient admitted to the cardiology intensive care unit on day 18 of hospitalization. Patients infected thereafter from other wards were at some point of their hospitalization transferred either to the cardiology ICU or the general ICU or were hospitalized during overlapping periods of time in the cardiology ICU with the index patient.	Other or not known
Maltezou, 2009[78]	2007-2008	Greece	Tertiary care hospital	KPC-2-producing *Klebsiella pneumoniae*	The first case occurred in May 2007 - the patient had no history of hospitalization. Overall, from May 2007 through May 2008, 23 patients with KPC-producing *K. pneumoniae* infections and available isolates for confirmation were identified.	Other or not known
Morris, 2012[79]	2011	Ireland	Two hospitals	KPC-2-producing *Klebsiella pneumoniae*	Hospital A: The index case was identified on 6th January 2011 and an outbreak was declared following a second case in the same unit on 24th January. In August 2011 a further isolate was detected in a patient from the community and in October an additional isolate was detected in a patient admitted to a ward implicated in the outbreak. Hospital B: In January 2011 carbapenem-resistant *K.pneumoniae* was also identified in a patient in the ICU of hospital B who had previously self-discharged from hospital A. One further case was identified on screening.	Other or not known

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
Ronayne, 2012[80]	2011	Ireland	General surgical wards	OXA-48 producing *Klebsiella pneumoniae*	Between January and October 2011, 13 isolates of OXA-48 producing *Klebsiella pneumoniae* (*K. pneumoniae*) were detected in the laboratory. The first five cases were found in clinical specimens of inpatients on general surgical wards.	Other or not known
Schaffer, 2012[81]	2011	Ireland	Tertiary care hospital	OXA-48 producing *Klebsiella pneumoniae*	From January to August 2011, 11 isolates of OXA-48 *K.pneumoniae* were detected in one hospital. There were 5 cases and 6 carriers. There was one further case identified retrospectively but this case had a different typing so was not thought to be related to the outbreak.	Other or not known
Wrenn, 2014[82]	2011	Ireland	Tertiary care referral centre	OXA-48-producing *Klebsiella pneumoniae*	The first three isolates were grown from clinical specimens taken from patients admitted to the three surgical wards in March and April 2011. In total sixteen OXA-48-producing *K.pneumoniae* isolates were detected, from both clinical and screening specimens. Typing analysis revealed that two outbreak strains were circulating in the hospital, one among surgical patients and one among medical patients.	Other or not known
Agodi, 2011[83]	2009	Italy	Intensive care unit	KPC-3-producing *Klebsiella pneumoniae*	The index patient had been transferred from another department 23 days before carbapenem resistant *K.pneumoniae* was identified. 24 KPC-3-Producing *Klebsiella pneumoniae* resistant isolates were recovered from 16 patients in the ICU	Other or not known
Gaibani, 2013[84]	2012	Italy	Not specified	*Citrobacter freundii* carrying VIM-1	From June 1 to June 15, 2012, eight isolates of *C. freundii* were isolated from rectal swabs of patients hospitalized on a medical ward of a hospital as a result of active screening following the detection of a KPC-positive patient on the same ward. All were colonized. Isolates were resistant to all b-lactams, b-lactam/b-lactamase inhibitor combinations, and imipenem.	Other or not known
Gaibani, 2014[85]	2010	Italy	Hospital-wide	Carbapenem-resistant *Klebsiella pneumoniae*	On 8th November, a carbapenems-non susceptible *K. pneumoniae* was isolated from a patient admitted to the Intensive Care Unit (ICU). Susequently, 11 carbapenems-non-susceptible Enterobacteriaceae have been isolated from 11 patients up to 19 days after the detection of the index case. Four out of 11 patients were	Other or not known

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
					hospitalized in the ICU.	
Giuffre, 2013[86]	2012	Italy	Neonatal intensive care unit	Carbapenemase-producing *Klebsiella pneumoniae*	KPC-Kp ST258 was detected by an active surveillance culture programme (in place since June 2009). Between 18th September and 14th November 2012, KPC-Kp was isolated from 10 out of 54 neonates admitted in the outbreak period. No cases of infection were recorded.	Other or not known
Mammina, 2012[87]	2011	Italy	Acute general hospital	Colstin-resistant *Klebsiella pneumoniae*	Between June and December 2011, 58 colistin-resistant *K. pneumoniae* isolates were recovered from 28 patients admitted to different wards, but mainly in the intensive care units. All but 6 isolates showed six isolates showed carbapenem resistance.	Other or not known
Mammina, 2010[88]	2009	Italy	Intensive care unit	Carbapenemase-producing *Klebsiella pneumoniae*	Between 9 April and 1 September 2009, 13 inpatients were colonized or infected.	Other or not known
Mezzatesta, 2011[89]	2010	Italy	Two hospitals	Colistin-resistant and carbapenem-resistant *Klebsiella pneumoniae*	Between August and October 2010, a hospital outbreak was caused by eight *K.pneumoniae* isolates from eight patients in two hospitals in Catania. A further three isolates were obtained from intestinal tract and pharyngeal colonization of three patients.	Other or not known
Nouvenne, 2013[90]	2011-2012	Italy	Sub-acute critical care ward	KPC-producing *Klebsiella pneumoniae*	During the first two months of the outbreak (Aug -Sep 2011), with the traditional contact isolation approach, 41 new cases (23 in first month and 18 in the second) were observed. The cases were limited to an average of 8 cases per month in the following 5 months, after activation of the cohorting approach. After the restoration of the usual contact isolation measures there was a new increase in incidence rates.	Other or not known
Anesi, 2015[91]	2013	Italy	Geriatric ward	KPC *Klebsiella pneumoniae*	The outbreak occurred from August to October 2013. Seven were treated for KPC *Klebsiella pneumoniae* infection and seven were found to be asymptomatically colonized (based on clinical and screening specimens)	Other or not known
Rossi, 2011[92]	2009-2010	Italy	University Hospital - ICU, medical ward and surgical ward	KPC-2-producing *Klebsiella pneumonia*	From December 2009 through December 2010, 59 patients were infected and 2 colonized by KPC-2-producing *K. pneumoniae*. PCR analysis showed a cluster of 57 strains. A single case patient, infected at a long-term facility, introduced the strain into the hospital.	Other or not known

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
Mena, 2006[93]	2005	Spain	Intensive care unit	ESBL-producing *Klebsiella pneumoniae* (including 2 cases with carbapenem resistance)	A total of 52 cases of ESBL-producing *K.pneumoniae* were documented in 2005. The outbreak started in February and reached its peak during May and June with 13 and 12 new cases respectively. In two of the patients infected by the epidemic multi-resistant *K. pneumoniae* clone, development of carbapenem resistance was documented.	Other or not known
Nieto-Gonzalez, 2010[94]	2009-2010	Spain	Intensive care unit	ESBL-producing *Klebsiella pneumoniae*	There were 7 infected and 6 colonised patients admitted to the unit between October 2009 and March 2010. The outbreak was caused by a single type of clone of ESBL-producing *K.pneumoniae*. The outbreak was caused by a single type of clone of ESBLKP resistant to all quinolones and cephalosporin's except cefoxitin. In two patients it was also found resistance to all carbapenems.	Other or not known
Olea Jimenez, 2013[95]	2011-2012	Spain	Intensive care unit	OXA-48 *Klebsiella pneumoniae*	82 patients had confirmed OXA-48 *K.pneumoniae*.	Other or not known
Pano-Pardo, 2013[96]	2010-2011	Spain	Hospital-wide	OXA-48-producing *Klebsiella pneumoniae*	From April 2010 to December 2011, 71 patients were identified to have OXA-48 KP in clinically guided cultures. Nine were considered to be colonising rather than causing infection. The peak incidence occurred in March 2011 (12 cases), then the number of incidence cases decreased.	Other or not known
Pitart, 2011[97]	2009-2010	Spain	Neurosurgical intensive care unit and hepatology ward	OXA-48 and CTX-M-15 producing *Klebsiella pneumoniae*	On 7 April 2009, a male (patient 2) was transferred to the neurosurgical intensive care unit (SICU) from the ICU of a hospital in Morocco. Two days later the first *K. pneumoniae* isolate producing OXA-48 carbapenemase was found from a patient in the same SICU (patient 1), whereas an OXA-48-producing *K. pneumoniae* isolate from patient 2 (presumably the index case) was not detected until 14 April 2009. During the subsequent period of time (April 2009 to September 2010), 18 more OXA-48-producing *K. pneumoniae* isolates were recovered.	Index patient with history of hospitalisation abroad

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
Robustillo Rodela, 2012[98]	2009-2010	Spain	Hospital-wide	KPC-3 carbapenemase-producing *Klebsiella pneumoniae*	From 16 September 2009 to 28 February 2010 seven patients infected or colonised with KPC-3-KP were detected.	Other or not known
Sanchez-Romero, 2012[12]	2009	Spain	Two intensive care units	VIM-1-Producing *Klebsiella pneumoniae*	During 2009, CNSKP isolates were obtained from clinical samples from 55 patients admitted to the ICUs	Other or not known
Vergara-Lopez, 2013[37]	2009-2011	Spain	Intensive care unit	Multidrug-resistant IMP-8 producing *Klebsiella oxytoca*	The outbreak occurred from March 2009 to November 2011 and evolved over four waves. Forty-two patients were affected. A contaminated sink drainage system was identified as the source of the outbreak.	Environmental reservoir
Madueno, 2014[99]	2013	Spain	General and digestive surgery unit	OXA-48-producing *Klebsiella pneumoniae*	The outbreak was detected between 19/10/2013 and 4/11/2013 in three patients admitted to general and digestive surgery unit, who coincided in time and space. Active screening detected 63 cases reported by 30/5/2014: 23 (36%) in clinical sample (only or with a rectal swab) and 40 (64%) in rectal swabs. Out of the clinical samples, 15 (65%) were classified as nosocomial infections, 4 (17.5%) nosocomial colonizations and 4 (17.5%) extra-hospital infections. Pulsed-field gel electrophoresis identified one main clone type.	Other or not known
Espasa-Soley, 2012[31]	2011	Not specified - assume Spain	Not specified	Carbapenem-resistant *Klebsiella pneumoniae* producing OXA-48 and CTX-M-15	The outbreak was linked to a duodenoscope contamination. In total, 12 patients were identified as carrying a KPCR from December 2010 to July 2011. All patients had been subjected to endoscopic retrograde cholangiography (ERC).	Contaminated hospital instrument
Lemmenmeier, 2014[100]	2013	Switzerland	Intensive care unit	KPC-2-producing *Klebsiella pneumoniae*	The outbreak took place in a medical intensive care unit between February and April 2013 and three severely ill patients were affected. Case 2, who was transferred from an Italian hospital, was suspected as the index patient.	Index patient with history of hospitalisation abroad
Dautzenberg, 2014[101]	2009-2011	The Netherlands	Hospital-wide	OXA-48 producing Enterobacteriaceae	Two cases of *K. pneumoniae* OXA-48;CTX-M15 diagnosed in one hospital on 31st May 2011. Outbreak investigation ensued.	Other or not known

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
Meessen, 2010[102]	Not stated	The Netherlands	TB-care facility	Carbapenem-resistant *Klebsiella pneumoniae*	The index case was a leukaemic patient admitted to the hospital. Screening of all patients in the TB-care facility where the patient initially stayed revealed another 6 patients with carbapenem-resistant *K. pneumoniae* (KPC-Kp). In total 13 other patients proved to be colonised with KPC-kp. Environmental cultures also yielded KPC-Kp.	Other or not known
Weterings, 2014[103]	2013	The Netherlands	Teaching hospital	Colistin-resistant carbapenemase-producing *Klebsiella pneumoniae*	The index was a patient who had been hospitalized on an ICU in Greece and was transferred in July 2013 to a pulmonary ward of a large Dutch teaching hospital. Despite contact isolation measures according to the national guidelines, a secondary case of KPC-KP was detected in a pleural fluid of a ward mate. Early August, the index patient was discharged to a rehabilitation ward of a nursing home (NH). Here, the patient was cared for in contact isolation. In November a third case of KPC-KP was found in a resident of the same ward as the index patient. Active contact screening revealed three other (rectal) carriers of KPC-KP. All isolates were resistant to carbapenems, colistin and all other groups of antibiotics tested.	Index patient with history of hospitalisation abroad
Poirel, 2014[104]	2013	Turkey	Hospital-wide	*Klebsiella pneumoniae* producing carbapenemases OXA-48, NDM-1 and KPC-2, Enterobacter cloacae isolates producing NDM-1, and Escherichia coli isolates producing OXA-48	Twenty-two consecutive carbepenem-resistant Enterobacterial isolates were recovered from patients hospitalized between January and April 2013 in different units in the hospital.	Other or not known
Thomas, 2013[105]	2008-2010	United Kingdom	Renal dialysis inpatients and outpatients	OXA-48 producing *Klebsiella pneumoniae*	Twenty carbapenem-intermediate or -resistant *K. pneumoniae* isolates were identified from 13 patients attending a teaching hospital between January 2008 and April 2010.	Other or not known
Koo, 2012[32]	2010	United Kingdom	Urology unit	NDM-1 *Klebsiella*	The outbreak involved 12 patients. The common source of infection was rapidly traced to the endoscopic video camera head in the urology theatre.	Contaminated hospital instrument
Davis, 2013[106]	2012-2013	Not specified - assume	Spinal injuries unit	Carbapenem resistant organisms (type not specified)	The outbreak affected seven patients on the unit. Spread occurred from August 2012 to June 2013 with transmission between patients initially suggested by	Other or not known

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
		United Kingdom			overlap in ward stay and later confirmed by plasmid sequence analysis of isolates. Currently all but one isolate have been associated with colonisation rather than infection.	
Verma, 2013[107]	2012	Not specified - assume United Kingdom	Pediatric liver transplant centre	blaVIM-4 Metallo-Beta-Lactamse producing Enterobacteriaceae (*Klebsiella pneumoniae* & *Klebsiella oxytoca*)	Identification of a positive patient led to implementation of surveillance for CPE with 11 further positive cases detected between September to December 2012.	Other or not known
Borgia, 2012[108]	2011	Canada	Intensive care unit (respirology and oncology wards)	NDM-producing *Klebsiella pneumoniae*	Five NDM-1–producing *K. pneumoniae* colonizing and/or clinically infecting patients in a community tertiary hospital were detected between October and November 2011	Other or not known
Lowe, 2013[109]	2011-2012	Canada	Tertiary care hospital	NDM-1 producing *Klebsiella pneumoniae*	There were 9 cases in total. Two index cases carrying NDM1-Kp with different PFGE patterns were identified. Nosocomial transmission to 7 patients (4 room-mates, 2 ward mates, and 1 environmental contact) was subsequently identified. The index patient for clone 1 had previously received health care in India. The index case for clone 2 had no previous travel to the Indian sub-continent	Index patient with history of hospitalisation abroad
Chandran, 2012[110]	2012	Canada	Tertiary care hospital	NDM-1 and OXA-48-producing *Klebsiella pneumoniae*	The index patient had a recent hospital admission in the Indian subcontinent. Index patient was placed in a 4-bed room upon admission, and 5 other cases ensued.	Index patient with history of hospitalisation abroad
Endimiani, 2009[111]	2008	United States	Long-term acute care hospital and three other hospitals	KPC-producing *Klebsiella pneumoniae*	Following the death of a patient who was found to have KPC-producing *Klebsiella pneumoniae* (blaKPC positive), over the subsequent 1 month period (21 March 2008–20 April 2008) all *K. pneumoniae* isolates showing reduced susceptibility to ertapenem were screened for the production of carbapenemases. Seven strains were isolated from patients at the hospital, and three from patients at different hospitals using the same laboratory.	Other or not known
Enfield, 2014[44]	2009-2011	United States	Intensive care unit	Carbapenemase-producing Enterobacteriaceae (type not specified)	A total of 49 patients were identified with CPE during the study period (April 2009 to September 2011). This was a dual outbreak of CPE and extensively drug-resistant	Other or not known

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
					Acinetobacter baumannii (XDR-AB).	
Epson, 2014[112]	2012	United States	Acute care hospital	NDM-producing carbapenem-resistant EnterobacteriaceaeEnterobacteriaceae	Two patients were initially identified with NDM-producing CRE during July–August 2012. A third case patient, admitted in May, was identified through microbiology records review. Surveillance identified 5 additional case patients. Of the total 8 patients 3 were infected and 5 colonized. The outbreak lasted 4 months before transmission was controlled.	Other or not known
Greene, 2011[113]	Not specified	United States	Long-Term Care Ventilator Unit	Carbapenemase-producing *Klebsiella pneumoniae*	Over a 3-week period, the organism was isolated from urine cultures on 3 separate patients. Analysis of pulse gel electrophesis (PFGE) indicated the same pattern on all 3 isolates. Subsequent surveillance cultures were obtained on all patients on the unit - 5 additional isolates from 3 of the other 7 patients were positive for the organism.	Other or not known
Marchaim, 2011[114]	2009	United States	Two hospitals and a long-term acute-care facility	Colstin-resistant carbapenem-Resistant *Klebsiella pneumoniae*	A cluster of five cases of colistin-resistant, carbapenem-resistant *K. pneumoniae* was identified from 27 July to 22 August 2009. All were from clinical cultures; none were from surveillance cultures.	Other or not known
Munoz-Price, 2010a[115]	2009	United States	Surgical intensive care unit	KPC-producing *Klebsiella pneumoniae*	Between 1st January 2009 and 1st January 2010 nine patients were either colonised or infected with KPC-producing *K.pneumoniae* in a 20-bed surgical intensive care unit. Of these, 6 patients died.	Other or not known
Munoz-Price, 2010b[45]	2008	United States	Long-term acute care hospital	KPC-producing *Klebsiella pneumoniae*	Between 1st January 2008 and 31st December 2008, 11 patients with positive results on clinical cultures were identified; 10 were patients who had KPC-negative surveillance culture results at admission. From January 1, 2008, until the intervention, 8 KPC-positive clinical cases—suspected to be due to horizontal transmission—were detected. From implementation of the intervention through December 31, 2008, only 2 KPC-positive clinical cases, both in August 2008, were detected.	Other or not known
Nadkarni, 2009[116]	2005	United States	Surgical and medical	KPC-2 producing *Klebsiella pneumoniae*	Between January and April 2005 a total of seven patients in the intensive care units at a 500-bed	Other or not known

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
			intensive care units		community-teaching hospital were noted to have *K.pneumoniae* bacteremia with reduced susceptibility to carbapenems. There were no specific rooms or locations in the SICU or MICU that were more likely to be affected. No breakdown in infection control measures has been identified.	
Palmore, 2013[117]	2011	United States	Hospital-wide	KPC-producing *Klebsiella pneumoniae*	From August to December 2011, the National Institutes of Health Clinical Center experienced an outbreak of carbapenem-resistant *Klebsiella pneumoniae* infections and colonization. The cluster began with the transfer of a patient from a New York City facility. Despite isolation measures implemented at the beginning of hospitalisation, transmission led to KPC-producing *Klebsiella pneumoniae* infections in 8 patients, 6 of whom died of infection, and colonization in 9 others. Seven months after the putative end of the outbreak, 1 additional patient acquired the bacteria through nosocomial spread and died from infection.	Other or not known
Rosenberger, 2011[118]	2009	United States	Intensive care unit	Carbapenem-resistant, gram-negative multi-drug-resistant organisms (including Enterobacteriacae)	Over a ten week period six patients on the ICU had infections with carbapenem-resistant, non-clonal gram-negative multi-drug-resistant organisms (namely *Klebsiella pneumoniae* , *Citrobacter freundii*, *Stenotrophomonas maltophilia*, *Aeromonas hydrophilia*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Providencia rettgeri*. Five of the six patients also had simultaneous isolation of vancomycin-resistant enterococci (VRE).	Other or not known
Snitkin, 2012[119]	2011-2012	United States	Clinical research hospital, mainly in the ICU	KPC-producing *Klebsiella pneumoniae*	Index patient known to be colonized with carbapenem-resistant *K.pneumoniae* was admitted to ICU from another Hospital in New York, and discharged on 15 July. Another case of KPC-*K.pneumoniae* was observed on August 5 cultured from a tracheal aspirate of patient 2. Both patients isolates belonged to the epidemic ST 258 *K.pneumoniae* lineage. Each week thereafter, until 1 Jan 2012 one new case of colonization or active infection with KPC-*K.pneumoniae* was detected with a total of 17 cases.	Other or not known

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
Alrabaa, 2013[17]	2008-2009	United States	Two tertiary hospitals	Carbapenemase-producing *Klebsiella pneumoniae*	Hospital A is a 206-bed cancer center, and hospital B is a 988-bed tertiary hospital. Seven cases of CRKP were identified. All 7 patients had endoscopic procedures at the same endoscopic center (facility C) within the prior 60 days. Forty-six of 51 patients who underwent ERCP procedures from January 2008 to January 2009 at this facility were invited for screening, and an additional 3 patients colonized with carbapenamse-producing organisms were identified.	Contaminated hospital instrument
Epstein, 2014[30]	2013	United States	Tertiary care hospital	New Delhi Metallo-β-Lactamase–Producing Carbapenem-Resistant *Escherichia coli*	In total, 39 case patients were identified during January 2013 to December 2013, 35 with duodenoscope exposure in 1 hospital. NDM-producing *Escherichia coli* was recovered from a reprocessed duodenoscope and shared more than 92%similarity to all case patient isolates by PFGE.	Contaminated hospital instrument
Chitnis, 2012[41]	2009-2011	United States	Long-Term Acute Care Hospital	Carbapenem-resistant Enterobacteriace (mainly *Klebsiella pneumonia*)	Ninety-nine CRE transmission cases (34 probable, 65 possible) were detected from March 1, 2009, through February 28, 2011. There were also 16 admission cases (from 7 acute care hospitals). 29 CRE bacteraemia episodes were identified.	Other or not known
Abdalla, 2014[120]	2013	Not specified - assume United States	Not specified	Carbapenem-resistant Enterobacteriacea (type not specified)	In 2013, the first CRE case was identified in the community. Six additional cases followed. Six out of the seven patients were found to be residents of a particular skilled nursing facility within a certain timeframe. Only one patient was found to be transferred from a metropolitan rehab facility to receive care locally. Despite the increase in CRE in the community and among admitted patients, the hospital maintained zero nosocomial CRE cases.	Other or not known
Sanderson, 2010[33]	2008-2009	Not specified - assume United States	Cancer treatment center	Carbapenem-resistant *Klebsiella pneumoniae*	In late 2008, three patients at a regional cancer treatment center were diagnosed with CRKP infection on or shortly after admission. Pulse-field gel electrophoresis (PFGE) patterns were identical in the three isolates. All three patients had recently received treatment at healthcare facilities in a nearby county. Investigations revealed a total of 13 cases. Six of the patients had undergone ERCP procedures with a common scope	Contaminated hospital instrument

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
					from June 2008 to January 2009. The endoscope was found to be contaminated - as a result, 46 of 51 patients who underwent ERCP procedures from January 2008 to January 2009 were tested and this revealed an additional three cases.	
Preas, 2011[121]	2010	Not specified - assume United States	Cardiac surgery intensive care unit	Multidrug resistant *Klebsiella pneumoniae*	During a 15 day period in January 2010, 5 patients in the unit had clinical cultures positive for a multidrug resistant *Klebsiella pneumoniae*. All isolates were sensitive to imipenem and Polymixin B, had variable susceptibility to amikacin and other carbepenems (resistant to ertapenem and susceptible or resistant to meropenem), and resistant to all other classes of antibiotics. Clinical infection was confirmed in 4 of 5 patients (the 5th patient was colonized). Eight of nine isolates were genetically identical, with one isolate found to be closely related strongly suggesting cross-transmission.	Other or not known
Adler, 2013[122]	2012	Israel	Neonatal intensive care unit	OXA-48-producing Enterobacteriaceae	Outbreak lasted from March 2012 until the last case of CPE carriage identified in December 2012, resulting in a total of 57 affected patients, including 16 with invasive infections	Other or not known
Ciobotaro, 2011[42]	2006-2010	Israel	Secondary care hospital	Carbapenem-Resistant *Klebsiella pneumoniae*	Study reports on the highly transmissible and virulent carbapenem-resistant *Klebsiella pneumoniae* (CRKP) KPC-3 strain has been spreading in the medical center (and in other centers in Israel) since 2006. The total number of cases not clearly reported as authors focus on changes in incidence overtime.	Other or not known
Nasser, 2014[123]	2011-2012	Israel	Sub-acute department	MDR *Klebsiella pneumoniae*	The alarm was raised when a death occurred and two cases were infected and reported with MDR *Klebsiella pneumonia*. Screening all admissions from other healthcare settings at the time revealed 65% of patients colonised with CPE.	Other or not known
Ben David, 2013[38]	2011-2012	Israel	Trauma unit	Carbapenemase-producing *Klebsiella pneumoniae*	Since 2007 the institution had an active surveillance program including rectal surveillance cultures obtained from patients hospitalized in intensive-care and step-down units upon admission and once weekly until	Environmental reservoir

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
					discharge. During September 2011 routine screening cultures identified 4 patients with carbapenemase-producing *Klebsiella pneumoniae* (CRKP) carriage. Infection control measures did not prevent continuous transmission of CRKP in the ward. Between October 2011 to February 2012, another 4 patients acquired CRKP. An investigation found that all colonized patients were nursed on the same mattress. Microbial swabbing revealed a high level of bacterial contamination of all mattress layers.	
Ben-David, 2010[39]	2006-2008	Israel	Tertiary care hospital	Carbapenem-resistant *Klebsiella pneumoniae*	In 2006, an outbreak of carbapenem-resistant *K. pneumoniae* infection spread throughout the Medical Center. Over the three year study period there were 390 patients with carbapenem-resistant *K. pneumoniae* colonization or infection.	Other or not known
Borer, 2011[40]	2006-2010	Israel	Tertiary care hospital	Carbapenem-Resistant *Klebsiella pneumoniae*	A total of 10,680 rectal cultures were performed for 8,376 patients during May 2006-May 2010; there were 433 (5.16%) CRKP-colonized and 370 (4.4%) CRKP-infected patients, respectively	Other or not known
Oved, 2009[124]	2007-2008	Israel	Acute care hospital	Carbapenem-Resistant *Klebsiella pneumoniae*	There were 77 CRKP carriers in 2007 and 12 in 2008.	Other or not known
Geffen, 2010[125]	2006-2009	Israel	Tertiary care hospital	Carbapenem-Resistant Enterobacteriace (mainly *Klebsiella pneumonia*)	In 2006, the prevalence of carbapenem-resistant (CR) KP isolates in the hospital increased significantly, rapidly becoming a major outbreak. During 2006–2007 all CRKP isolates at the institution were found to carry the blaKPC gene. Approximately 90% of these isolates contained the KPC-2 allele and 10% contained the KPC-3 allele. Pulsed-field gel electrophoresis (PFGE) revealed one major Xba1 endonuclease-restricted DNA profile in 90% of the CRKP isolates. During the study period (2008-2009), 229 CRE carriers were identified in 2008 and 144 in 2009)	Other or not known

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
Cohen, 2011[43]	2006-2010	Israel	Tertiary care hospital	Carbapenem-Resistant *Klebsiella pneumoniae*	From January 2006 through August 2010, a total of 335,703 patients were admitted, of whom 603 patients; 410 (68%) had in-hospital acquisition and 197 (32%) had acquisition prior to hospital admission.	Other or not known
Balkhy, 2012[126]	2010	Saudi Arabia	Tertiary care hospital adult intensive care unit	Carbapenem-resistant *Klebsiella pneumoniae*	During March 2010, a cluster of eight CRKPs was detected primarily in the adult intensive care unit (ICU). In the year between September 2009 and August 2010, 20 (1.17%) out of 1,706 *K. pneumoniae* isolates detected at the medical facility were CRKP. Two-fifths of patients had clinical infection.	Other or not known
Dai, 2014[34]	2011	China	Neurosurgical unit	Carbapenemase-producing *Klebsiella pneumonia*	During July 2011 an outbreak of neurosurgical site infections with carbapenemase-producing *Klebsiella pneumonia* occurred. The outbreak affected 7 patients. Subsequent investigation revealed that a barber's contaminated shaving razor may have caused the outbreak	Contaminated hospital instrument
Pang, 2014[127]	2010-2012	China	Hospital-wide	IMP-producing Enterobacteriaceae	Between November 2010 and September 2012 CPEs were isolated from the four distinct orthopaedic patients, three patients infected with *E. cloacae* and one with *K. oxytoca* infection. Four patients had invasive surgical procedures. All patients were cured and discharged, without outbreak of nosocomial infection caused by CPE. Environmental sampling did not detect CPE.	Other or not known
Wenjun, 2013[128]	2011	China	Intensive Care Unit	KPC-2-producing *Klebsiella pneumoniae*	Between October and December 2011, 27 *K. pneumoniae* isolates were collected from nine patients and their different sites and their surrounding environment. Multi-locus sequence typing analysis indicated all isolates belonged to the ST11 clone.	Other or not known
Fukigai, 2007[129]	2003-2004	Japan	General hospital	IMP-1 beta-lactamase-producing *Klebsiella pneumoniae*	From February 2003 to June 2004, 456 clinical isolates of *K.pneumoniae* were obtained from patients. Six isolates were confirmed as MBL-producing strains.	Other or not known
Chae, 2014[130]	2013	South Korea	Secondary care hospital	OXA-232 carbapenemase-producing *Klebsiella pneumoniae*	Seven OXA232 KP and one non-carbapenemase-producing carbapem-resistant *K.pneumonia* (non-CPCRKP) were detected from 9 samples from May 15th to July 2013.	Index patient with history of hospitalisation abroad

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
Carrilho, 2011[131]	2009-2010	Brazil	Hospital-wide	Mainly KPC-2	The outbreak began on February 2009 with 19 cases, decreased to one case in June 2009 after control measures were instigated. On July 2009 there were new cases, despite control measures, and there are now around 21 new cases each month. The infection is becoming endemic in the hospital.	Other or not known
Pereira, 2013[132]	2008-2010	Brazil	Hospital-wide	Carbapenem-resistant *Klebsiella pneumoniae*	During the period from October 2008 to December 2010, there were 33 cases of infections caused by carbapenem-resistant *Klebsiella pneumoniae*. Infections were caused by five different genotypes, three of which presented a clonal distribution. Genotype B was identical to isolates from 11 other hospitals in São Paulo. Sixteen of the 33 patients (48%) died during hospitalisation.	Other or not known
Zavascki, 2012[133]	2008	Brazil	Intensive care unit	Carbapenem-resistant *Providencia stuartii*	Patients who had a CRPS isolate recovered from April 2008 (index case) to June 2008 were included in the study. In total, 11 isolates from 5 patients were recovered during the study period.	Other or not known
Escobar Perez, 2013[134]	2012	Columbia	Neonatal unit	NDM-1-producing *Klebsiella pneumoniae*	Six multi-resistant, NDM-1-producing *Klebsiella pneumoniae* strains were recovered from an outbreak that affected six neonatal patients	Other or not known
Gregory, 2010[10]	2008	Puerto Rico	Tertiary care teaching hospital	Carbapenem-resistant *Klebsiella pneumoniae*	Twenty-six patients were identified during the outbreak period of February through September 2008.	Other or not known
Ingold, 2012[135]	2011	Uruguay	Intensive care unit	KPC-producing *Klebsiella pneumoniae*	Four *K. pneumoniae* isolates were recovered in March and April 2011 from two intensive care unit (ICU) patients	Other or not known
Marquez, 2014[136]	2011	Uruguay	Intensive care unit	KPC-producing *Klebsiella pneumoniae*	Two patients were identified in February/March 2011.	Other or not known
Herbert, 2007[137]	2004-2005	Australia	Tertiary care hospital	Multiple genera of gram-negative bacilli carrying the metallo-b-lactamase gene blaIMP-4	The outbreak began in the intensive care unit, with sixty-two patients had an MBL-producing organism isolated from a clinical sample hospital-wide.	Other or not known
Kotsanas, 2013[35]	2009-2012	Australia	Intensive care unit	Carbapenem resistant Enterobacteriacea (several types)	Four clusters of gram-negative bacteria harbouring the MBL gene blaIMP-4 were detected in the ICU at	Environmental reservoir

Author, publication year	Year of outbreak	Country	Hospital setting	CPE type	Brief description of outbreak	Likely source of outbreak
					Dandenong Hospital between November 2009 and July 2012. There were 10 clinical isolates and one screening isolate.	
de Jager, 2015[138]	2011-2012	South Africa	Adult intensive care unit	NDM-1-producers, mainly *Klebsiella pneumoniae*	The outbreak occurred in three private hospitals but the paper focusses on just one of these. In early August 2011 *Klebsiella pneumoniae* isolated from an 86-year-old male was found to harbour blaNDM-1. In response, a rectal screening programme was instituted to identify patients colonised with NDM-1-producers.	Other or not known

Table II. Type of infection control measures used and percieved effectiveness (ordered by geographic area, as per Table I)

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
Leitner, 2014[36]		✓	✓			✓•	✓				Since October 2013, no more KPC-producing *K. oxytoca* isolates have been identified	Yes
Novak, 2014[63]	✓				✓		✓				Authors conclude that the outbreak highlights the need for continued surveillance of carbapenem resistance, strict implementation of a multidisciplinary panel of infection control measures and wiser antibiotic policies.	Unclear
Kanerva, 2014[64]	✓				✓		✓		✓	✓	The outbreak was confined to one ward. Authors state that up to December 2013, there were no new cases.	Yes
Carbonne, 2010[18]	✓			✓	✓	✓•	✓				As of 1 November 2010, no new case involving the same strain was identified in these seven hospitals. Authors conclude that it is possible to limit cross-transmission of multidrug-resistant bacteria by healthcare workers in a multi-hospital setting by implementing systematic investigation and extended control measures	Yes
Cuzon, 2011[65]	✓			✓			✓				Not clear but it seems that cases continued to occur after instigation of control measures	No

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
Kassis-Chikhani, 2010[66]	✓	✓	✓	✓	✓	✓	✓		✓	✓	Authors state that systematic screening for IR-Kp of all patients admitted to the care centre is still maintained to date and no secondary IR-Kp case has been detected since 2 June 2004. Note that the outbreak was only halted after the additional control measures were applied. Authors conclude that extended control measures are adequate to control outbreaks of emerging multi-resistant organisms, particularly in countries where the incidence is very low.	Yes
Levast, 2011[67]	✓		✓								Not clear but no further cases are reported	Unclear
Semin-Pelletier, 2015[68]	✓			✓	✓		✓				There was some evidence that triple cohorting brought the epidemic under control, on two occasions.	Unclear
Ducomble, 2015[69]	✓			✓	✓		✓		✓		Although the outbreak was partially contained, 22 further cases were detected after July 2012, the last of which was detected in April 2013. The authors state that the number of cases could have been underestimated by only including isolates with the identical PFGE patterns in the investigation.	No
Kola, 2015[15]	✓	✓	✓	✓	✓						The outbreak ended after the endoscope was sent to the manufacturer for	Yes

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
											maintenance.	
Lubbert, 2013[70]	✓		✓	✓	✓		✓		✓	✓	Authors state that the last case was detected in April 2013, and that successful containment of the outbreak was related to the implementation of an overarching concept of infection control	Yes
Steinmann, 2011[71]	✓	✓	✓	✓	✓	✓	✓			✓	The measures introduced seem to have been effective. Peri-anal screening was set up as a result of this outbreak and so CPE resistance is now being routinely monitored.	Yes
Wendt, 2010[58]	✓		✓		✓					✓	The last patient associated with the outbreak left the hospital in June and no additional cases were detected during the following six months. The authors conclude that the outbreak was considered to have been terminated.	Yes
Douka, 2015[72]			✓	✓	✓	✓•	✓			✓	Authors state that the outbreak was ultimately interrupted - no further PDR *P. stuartii* strain was isolated 1 year after identification of the last case. However, of note it took a year to control the outbreak.	Yes
Karampatakis, 2012[73]			✓	✓	✓						Authors state despite control measures today the average of isolated cases is around four new cases monthly, becoming endemic in the hospital.	Unclear

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	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
Papadomichelakis, 2009[74]	✓			✓	✓		✓			✓	Authors conclude that the outbreak seems to be getting into an endemic status. Although transmission in the ICU seems to be more or less controlled, increased admissions of unidentified carriers, detection delays until cohorting and low nurse-to-patient ratios seem to be major obstacles to outbreak control.	Unclear
Souli, 2010[75]	✓	✓		✓	✓	✓	✓		✓	✓	Authors stated that containment of the outbreak was due to their measures. However, the outbreak was still ongoing at the end of the study period.	No
Voulgari, 2014[76]					✓	✓	✓			✓	The authors state that the likelihood of novel carbapenemase genes disseminating in endemic areas and yet remaining undetected due to insufficient molecular epidemiological screening is clearly highlighted. Efficient identification was achieved with the implementation of stricter epidemiological surveillance that included collaboration between peripheral hospitals and reference centres.	Unclear
Voulgari, 2013[77]	✓				✓	✓	✓				The authors conclude that following the initial detection and characterization of this clone, infection control measures were reinforced and no novel OXA-48-possessing isolates have been reported to date.	Yes

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	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
Maltezou, 2009[78]		✓	✓		✓	✓•	✓	✓		✓	Authors report that from June 2008 until submission of the manuscript, one additional case occurred in this hospital. They also note that the outbreak extended for more than 12 months with documented ongoing transmission.	No
Morris, 2012[79]	✓				✓	✓	✓		✓	✓	Authors conclude that stringent enforcement of infection and prevention control and antimicrobial stewardship measures appear to have been effective in the termination of this specific outbreak.	Yes
Ronayne, 2012[80]	✓	✓	✓		✓	✓		✓			Not clear.	Unclear
Schaffer, 2012[81]	✓	✓	✓		✓	✓		✓			Following control measures there were two new cases. It is not clear when the carriers were identified.	No
Wrenn, 2014[82]	✓		✓	✓	✓	✓	✓	✓		✓	The authors report that the outbreak on surgical wards was successfully controlled by implementing strict contact precautions and rectal surveillance screening on the affected wards. The last surgical isolate was detected in September 2011 and no further isolates have been detected since.	Yes
Agodi, 2011[83]	✓			✓	✓	✓•	✓			✓	The outbreak was ultimately controlled within a 4-month period of time, with no novel carbapenem resistant isolates being	Yes

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
											detected thereafter. Authors conclude that reinforced infection control measures and strict monitoring of the staff adherence were necessary for the control of the outbreak.	
Gaibani, 2013[84]	✓			✓	✓					✓	Authors state that early and intensive action allowed containment of the cluster and no more cases were detected starting from June 16, 2012. The screening activity was continued for an additional 4 weeks, and no more *C. freundii* bearing blaVIM-1 were identified.	Yes
Gaibani, 2014[85]	✓		✓				✓			✓	During the two months after the outbreak no KPC-producers were detected during the active surveillance program implemented in different wards where infected and colonized patients were hospitalized.	Yes
Giuffre, 2013[86]	✓	✓	✓	✓	✓	✓	✓	✓		✓	On 21st November, only the third colonized neonate was still proven to carry KPC-Kp. There were no further cases of colonization or infection by CRE in the NICU during the following seven months. Note, that the outbreak was only halted after additional measures were applied.	Yes
Mammina, 2012[87]				✓	✓	✓	✓			✓	Authors state that despite the control measures, the outbreak developed further, and additional isolates were detected. The outbreak peaked in July and August 2011,	No

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	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
											but new cases occurred in the following months. In December 2011, three new cases were still recognised.	
Mammina, 2010[88]	✓			✓	✓						The outbreak was eventually controlled by September 2009.	Yes
Mezzatesta, 2011[89]	✓		✓		✓						No further cases reported.	Yes
Nouvenne, 2013[90]	✓		✓	✓							Authors conclude mortality in this setting was lower than that described in the literature. Staff cohorting isolation measures may be effective to limit the epidemic spread, although a periodicity in KPC infections cannot be excluded.	Unclear
Anesi, 2015[91]	✓		✓		✓	✓•	✓			✓	Authors conclude that the outbreak was ultimately controlled within a 3-month period of time, with no novel carbapenem-resistant isolates being detected thereafter.	Yes
Rossi, 2011[92]	✓				✓		✓			✓	Authors state that before the introduction of control program 9-11 patients/month were infected by KPC-2-producing K. pneumoniae. After the application of the control program a reduction of KPC-2-producing isolates was observed: in October 10 patients, in November 3 patients, in December 1 patient.	Yes

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	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
Mena, 2006[93]	✓		✓								The outbreak was still not considered to be under control by the end of 2005 as new cases were detected in the December of that year.	No
Nieto-Gonzalez, 2010[94]	✓		✓	✓			✓				The authors conclude that the death rate for this outbreak was low (1 patient) and that infection control measures helped to minimise the consequences.	Unclear
Olea Jimenez, 2013[95]	✓			✓	✓	✓	✓			✓	The outbreak was controlled in October 2012 and the authors conclude that isolation measures, exclusive personal hygiene, proper treatment and selective digestive decontamination controlled the difficult outbreak.	Yes
Pano-Pardo, 2013[96]	✓		✓	✓	✓	✓	✓		✓	✓	The authors state that to date, OXA-48 KP-infected/colonised patients continue to be identified. In spite of the duration and the widespread distribution of the cases, they believe that this set of cases represents a cluster of outbreaks associated with an outbreak of a major high-risk clone rather than an endemic situation, encouraging current efforts to intensify surveillance and strict compliance with standard and contact precautions.	Unclear

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
Pitart, 2011[97]	✓				✓	✓	✓				Authors conclude that the implementation of control measures led to the successful control of the outbreak.	Yes
Robustillo Rodela, 2012[98]	✓	✓	✓		✓	✓	✓			✓	After implementing the control measures, no further cases were reported in the affected units.	Yes
Sanchez-Romero, 2012[12]	✓		✓	✓	✓		✓			✓	Incidence rate lowered from 16.1 and 6.1/1,000 patient days (SICU and MICU) to 4.4/1,000 patient days. Specific interventions were highlighted as being effective for a short period after they were implemented but could not be sustained because of cost.	Unclear
Vergara-Lopez, 2013[37]	✓	✓	✓	✓	✓	✓	✓		✓	✓	The authors felt that the elimination of the horizontal drainage system finally eradicated the outbreak.	Yes
Madueno, 2014[99]	✓				✓					✓	Not clear.	Unclear
Espasa-Soley, 2012[31]	✓	✓			✓	✓•	✓				Authors state that rapid identification of outbreak cases and their source followed by implementation of strict infection control measures stopped the appearance of new cases related to the duodenoscope procedure.	Yes

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
Lemmenmeier, 2014[100]	✓		✓	✓	✓	✓•	✓			✓	Authors state that the outbreak was rapidly controlled.	Yes
Dautzenberg, 2014[101]	✓	✓	✓		✓	✓	✓			✓	No nosocomial transmission of Enterobacteriaceae OXA-48 was detected after 18 July 2011. The last presumed outbreak-related KP OXA-48 was detected in April 2012. Authors conclude that their findings suggest that contact isolation measures using single rooms with individual sanitary facilities attributed to controlling transmission.	Yes
Meessen, 2010[102]	✓	✓	✓	✓		✓					Authors concluded that strict infection control measures are effective.	Yes
Weterings, 2014[103]	✓	✓	✓	✓	✓		✓				Authors state that this pan-resistant KPC-KP spread repeatedly despite isolation measures. The outbreak was controlled by separating the KPC-KP positive residents in a separate building and by providing dedicated nursing staff.	Yes
Poirel, 2014[104]	✓	✓			✓					✓	After 30 to 45 days, there were no patients in the NICU who were infected or colonized with any CRE organism, and there has not been a single case since then (8 months).	Yes
Thomas, 2013[105]	✓	✓			✓	✓	✓		✓	✓	The authors feel the measures contributed to the decrease in cases from 2010 onwards.	Yes

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	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
Koo, 2012[32]	✓	✓				✓•				✓	Authors report that the measures taken successfully halted the outbreak. They also note that all infected patients and potentially exposed patients remain under close microbiological surveillance, and there have not been any further new transmitted cases since.	Yes
Davis, 2013[106]	✓		✓		✓						No information.	Unclear
Verma, 2013[107]	✓	✓	✓		✓	✓	✓		✓		Outbreak was contained in 3 months.	Yes
Borgia, 2012[108]	✓		✓		✓	✓•					Authors conclude that standard infection control practices, including active screening were able to contain the spread of the organism.	Yes
Lowe, 2013[109]	✓	✓			✓	✓•	✓			✓	Authors conclude that the implementation of infection control precautions contributed to the interruption of subsequent spread of the organism with no further transmission of NDM1-Kp identified since February 2012.	Yes
Chandran, 2012[110]	✓		✓		✓	✓		✓			Outbreak was declared over in May 2012.	Yes
Endimiani, 2009[111]	✓		✓	✓	✓						Authors state that after enhanced infection control practices were implemented, the outbreak was brought under control, with only one transmission of KPC-Kp infection	Yes

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
											after early April 2008. They conclude that active surveillance and enhanced infection control practices terminated the outbreak.	
Enfield, 2014[44]	✓	✓		✓	✓	✓•	✓		✓	✓	Incidence rate (IR) of CPE for the 12 months before the implementation of enhanced measures was 7.77 cases per 1,000 patient-days, and decreased to 1.22 cases per 1,000 patient-days (p=0.001) after.	Yes
Epson, 2014[112]	✓			✓	✓		✓			✓	Authors state that timely surveillance cultures, combined with targeted infection control measures, were likely responsible for controlling transmission.	Yes
Greene, 2011[113]	✓					✓	✓			✓	The bi-weekly surveillance did not identify any new cases.	Yes
Marchaim, 2011[114]	✓		✓	✓	✓		✓			✓	Authors state that no further cases of colstin-resistant carbapenem-resistant *Klebsiella pneumoniae* were identified.	Yes
Munoz-Price, 2010a[115]	✓	✓	✓	✓	✓	✓				✓	Authors conclude that the bundle of interventions successfully controlled the further horizontal spread of the organism.	Yes
Munoz-Price, 2010b[45]	✓	✓	✓	✓	✓	✓				✓	Authors conclude a bundled intervention was successful in preventing horizontal spread of KPC-producing *K.pneumoniae* in a long-term acute care hospital, despite ongoing admission of patients colonized with KPC	Yes

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
											producers.	
Nadkarni, 2009[116]					✓		✓		✓		It was concluded that infection control strategies were eventually successful in curbing the outbreak in April 2005.	Yes
Palmore, 2013[117]	✓	✓	✓	✓	✓	✓	✓			✓	Authors conclude that the strategy and associated improvement in hand hygiene and adherence to infection control precautions, led to conclusion of the outbreak. They believe that implementing infection control precautions that have been recommended by CDC, such as hand hygiene, cohorting, and active surveillance, most likely contributed the most, and remediation of environmental contamination the least, to the success.	Yes
Rosenberger, 2011[118]	✓			✓	✓		✓			✓	Two-months after the super-isolation procedures and all six patients had been discharged there were no new cases of multi-drug resistant infections.	Yes
Snitkin, 2012[119]	✓	✓	✓	✓	✓	✓	✓			✓	The authors feel that the outbreak was ultimately controlled by the strict IC measures.	Yes
Alrabaa, 2013[17]	✓	✓			✓	✓	✓			✓	Authors state that they report early identification and control of this outbreak.	Yes

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
Epstein, 2014[30]	✓	✓				✓•					Authors state that no new patients with duodenoscope-associated NDM were identified among patients who only had a procedure with a duodenoscope following the change to gas sterilization.	Yes
Chitnis, 2012[41]	✓			✓	✓	✓•	✓			✓	During the study period significant reductions were observed in CRE prevalence (49% vs 8%) and the percentage of patients screened with newly detected CRE (44% vs 0%).	Yes
Abdalla, 2014[120]	✓		✓	✓						✓	Not clearly specified but there were no nosocomial transmissions.	Yes
Sanderson, 2010[33]	✓	✓								✓	No information.	Unclear
Preas, 2011[121]					✓	✓•	✓				Heightened attention to hand hygiene, environmental cleaning and the disinfection of reusable patient care equipment were critical control measures in preventing further MDRKP transmission without the need for cohorting, dedicated staffing or intensified isolation precautions.	Yes
Adler, 2013[122]	✓			✓		✓	✓	✓			During the first week of the intervention, 8 new cases were identified in the NICU (7 surveillance, 1 clinical). Two additional new carriers were identified in the next month who were all previously exposed. Incidence of CPE acquisition declined to 5 cases in the	Yes

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
											first 4 months, followed by no new cases in the next 3 months. Authors conclude that while standard infection control measures are effective for initial containment, continuous vigilant monitoring is essential in order to detect and respond to a resurgence of the outbreak.	
Ciobotaro, 2011[42]	✓			✓	✓	✓•			✓	✓	The incidence of CRKP decreased by 16-fold (P <0.001), and this decrease was sustained for 30 months. The rate of cross-infection decreased from 6% during 2007-2008 to 2.7% in 2009-2010 (P<0.05). Authors conclude that a comprehensive infection control program can contain an outbreak of the CRKP KPC-3 strain in acute care hospitals during a nationwide outbreak of this strain.	Yes
Nasser, 2014[123]	✓				✓	✓	✓			✓	A downward trend of positive screening results over time reflected the efficacy of measures and new cases were screened on admission systematically and followed up accordingly. The authors conclude that a multidisciplinary effort supported by management and effective communication resulted in the control of the outbreak.	Yes

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
Ben David, 2013[38]	✓	✓	✓								Authors state that after discarding the damaged mattresses, a significant decrease in acquisition rate in the ward was observed, and since June 2012 no further patients have acquired CRKP.	Yes
Ben-David, 2010[39]	✓				✓						The incidence of clinical infection with carbapenem-resistant *K. pneumoniae* has decreased 4.7-fold, from 6.93 cases per 10,000 patient-days during the last quarter of the pre-intervention period to 1.8 cases per 10,000 patient-days during the last quarter of the intervention period (P<0.001).	Yes
Borer, 2011[40]	✓		✓	✓	✓	✓•	✓		✓	✓	From May 2006 through April 2007 (pre-intervention), the CRKP-infection incidence density per 10,000 patient-days was 5.26. After the intervention, the incidence density was reduced to2.91 in December 2007, followed by 1.91, 1.28, and 0.18 in 2008, 2009, and January-May 2010, respectively. No nosocomial CRKP infections were diagnosed in the more recent period.	Yes
Oved, 2009[124]	✓			✓	✓				✓	✓	A significant reduction in the incidence of new carriers from 77 in 2007 to 12 in 2008 was observed. Authors conclude that strict isolation precautions enforced at the institutional level and organization of multifaceted collaborative work of all	Yes

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
											professions involved in patient care can contain an outbreak in an acute care hospital even in an endemic country.	
Geffen, 2010[125]	✓				✓						The proportion of screened patients with CPE carriage decreased during the study period - from 11.6% in 2008 to 7.4% in 2009. Authors conclude that the implementation of a rapid, reliable CRE screening programme, combined with strict isolation precautions, successfully reduced the incidence rate of CRE in the institution.	Yes
Cohen, 2011[43]	✓		✓	✓	✓	✓•	✓			✓	Authors conclude that cohorting of patients with dedicated staff, combined with implementation of focused active surveillance, effectively terminated the epidemic spread of CRKP.	Yes
Balkhy, 2012[126]	✓	✓		✓	✓	✓	✓			✓	Authors conclude that reinforcing infection control measures together with contact isolation of patients colonized or infected with CRKP were successful in controlling the outbreak, but did not prevent endemicity.	Yes
Dai, 2014[34]	✓	✓	✓	✓	✓	✓				✓	After institution of infection control measures, no further patients were infected with CPKP	Yes

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
Pang, 2014[127]		✓	✓	✓	✓		✓			✓	Ultimately, all patients were cured and discharged. The authors conclude that the results underscore the importance of strict infection control measures to limit dissemination. In addition, reasonable support for treatment and disinfection protection seemed to be more effective for the infection of IMP-producing Enterobacteriaceae.	Yes
Wenjun, 2013[128]	✓	✓									Authors state that over a period of almost 10 months no further CPE were isolated.	Yes
Fukigai, 2007[129]					✓		✓		✓		Since June 2004, ceftazidime-resistant *K.pneumoniae* has not been isolated from the ward which housed patients with MBL-producing *K. pneumoniae*.	Yes
Chae, 2014[130]	✓	✓	✓			✓•		✓			Authors state that no further cases were identified to date.	Yes
Carrilho, 2011[131]			✓	✓	✓			✓			Following an initial decline to just one case in June 2009, control measures were not sufficient to control CPE which is becoming endemic in the hospital.	Unclear

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
Pereira, 2013[132]	✓				✓						The introduction of new clones on different occasions led to patient-to-patient spread and caused additional control measures to be necessary. The control measures were adopted to avoid an outbreak, but authors state that several introductions of new strains coming from other hospitals may have made control difficult. The authors also state that genotype B seems to have caused a state-wide spread and has persisted in their hospital despite the control measures.	No
Zavascki, 2012[133]			✓		✓	✓					The authors report that the outbreak was small, had a short duration, and was interrupted <3 months after the index case identification, only with the adoption of contact precaution measures.	Yes
Escobar Perez, 2013[134]	✓			✓	✓	✓•	✓	✓		✓	Authors state that measures instigated controlled the spread of the identified clone. No new cases were found in the unit during the 3 months following the last isolation.	Yes
Gregory, 2010[10]	✓			✓	✓		✓	✓	✓	✓	Authors conclude that once staff initiated active surveillance, cohorted patients, and placed them in contact precautions, they were able to control the outbreak quickly.	Yes
Ingold, 2012[135]	✓		✓	✓		✓		✓			No new cases were detected up to September 2011.	Yes

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
Marquez, 2014[136]	✓		✓	✓	✓	✓•	✓	✓		✓	Five months after the identification of the two case patients two colonized cases were detected. Authors state that similar control measures were applied, surveillance cultures were performed during the next 6 months and no more cases have been identified since then.	Yes
Herbert, 2007[137]			✓		✓	✓	✓		✓	✓	Authors note that there was a hospital-wide decline in the prevalence of MBL-producing organisms, and state that the use of gloves, gowns, and improved compliance with hand gel use probably limited cross-transmission between patients. However, 6 new cases of infection were identified in ICU in the 8 months following the study period.	Unclear
Kotsanas, 2013[35]	✓	✓				✓•					Authors conclude that attempts at sink sterilisation were futile, and complete eradication will require future sink removal and replacement with appropriately designed sinks.	No
de Jager, 2015[138]	✓		✓	✓			✓			✓	Authors conclude that controlling the outbreak was resource intensive and demanded a concerted effort from all role-players, with critical review of the outbreak situation and re-evaluation of interventional strategies throughout. Although sporadic cases of colonisation or infection with NDM-	Yes

Author, publication year	Control measures*										Effectiveness of control measures / authors conclusions	Do control measures appear effective?
	Screening / surveillance of patients (e.g. on admission, all inpatients)	Other screening (e.g. staff screening, environmental screening)	Patient isolation	Cohorting (of infected patients) and/or staff	Contact precautions (e.g. gloves, gowns)	Enhanced environmental cleaning/ decontamination	Handwashing intervention e.g. encouraged, monitored	Closure of ward or unit or hospital to new admissions	Antimicrobial stewardship / restricting use	Staff education/compliance monitoring		
											1-producers continue to be reported, no clusters or epidemiologically-linked cases have been identified since the end of the outbreak.	
Total	**85**	**35**	**51**	**52**	**78**	**56**	**61**	**13**	**18**	**57**		

*Includes all control measures reported to have been used (including any that may have been in place prior to the outbreak, if documented)
•Details on enhanced cleaning procedures (e.g. types of chemicals used) are provided in the original paper

Table III. Newcastle-Ottawa risk of bias assessments

Domain	Enfield, 2014[44]	Munoz-Price, 2010b[45]	Ben-David, 2010[39]	Borer, 2011[40]	Ciobotaro, 2011[42]	Chitnis, 2012[41]	Cohen, 2011[43]
Selection category							
Representativeness of the exposed cohort	*	*	*	*	*	*	*
Selection of the non-exposed cohort	*	*	*	*	*	*	*
Ascertainment of exposures	*	*	*	*	*	*	*
Outcome of interest not present at start of study		*				*	*
Total stars for selection category	***	****	***	***	***	****	****
Comparability category							
Cohort comparability based on design or analysis							
Total stars for comparability category							
Outcome category							
Assessment of outcome	*	*	*	*	*	*	*
Follow-up long enough for outcomes to occur	*	*	*	*	*	*	*
Adequacy of follow-up of cohorts							
Total stars for outcome category	**	**	**	**	**	**	**

Notes: A maximum of four stars can be awarded for ‘Selection’, two stars for ‘Comparability’, and three stars for ‘Outcome’. Blank boxes indicate that no star was awarded for that domain

Table IV. Effectiveness of CPE control measures during outbreaks in acute settings

Author, publication year	Type of study	Control measures used in comparator group	Control measures used in intervention group	Outcome measure	Outcome in comparator group (e.g. CPE rate or number of cases)	Outcome in intervention group (e.g. CPE rate or number of cases)	Supporting statistics
Enfield, 2014[44]	Before-after intervention study (interrupted time series analysis)	Infection control measures described in the Centers for Disease Control and Prevention (CDC) 2012 CPE toolkit were instigated. Before the intervention, routine infection control measures for patients with CPE included standard precautions (hand hygiene before and after patient care) and contact precautions (gown and glove barrier precautions). In addition, healthcare provider and patient education regarding CPE was provided, and the CPE status was marked in the electronic medical record. Rooms were cleaned with a quaternary ammonium compound, and all disposable items, curtains, and linens were removed after patient transfers.	The intervention included the following bundled interventions: weekly education and status update meetings, hand hygiene and contact isolation reinforced through signage and incorporation into ongoing quality efforts (e.g. patient care rounds), patients with CPE were cohorted in adjacent rooms, nursing and respiratory care were cohorted, daily patient baths using 2% chlorhexidine gluconate wipes were initiated, and pre-emptive contact isolation was used until a patient was proven not to be colonized with CPE or extensively drug-resistant *Acinetobacter baumanni* (XDR-AB) through surveillance cultures. Carbapenem antibiotics became restricted on the hospital formulary. All rooms underwent terminal cleaning within 48 hours of implementation of the intervention and whenever a patient with CPE or XDR-AB was discharged from the unit. Environmental services and nursing created a shared worklist defining responsibility for daily cleaning of all items in patient care rooms. Use of appropriate disinfectants with the manufacturers' recommended contact dwell times was reinforced. To assess the quality of environmental cleaning, adenosine tri-phosphate (ATP) bioluminescence testing was performed. Hand hygiene compliance was measured through a covert observation program that has been used in the setting since 2006.	Incidence rate of CPE	Incidence rate (IR) of CPE for the 12 months before the implementation of enhanced measures was 7.77 cases per 1,000 patient-days	IR was 1.22 cases per 1,000 patient-days after the intervention	Test for trend over time: p=0.001. No degradation of this decrease was observed over the 17 months after implementation in the segmented regression analysis (p=0.96).

Author, publication year	Type of study	Control measures used in comparator group	Control measures used in intervention group	Outcome measure	Outcome in comparator group (e.g. CPE rate or number of cases)	Outcome in intervention group (e.g. CPE rate or number of cases)	Supporting statistics
Munoz-Price, 2010b[45]	Quasi-experimental study	Not documented aside from a baseline point prevalence surveillance	The infection control bundle covered: decolonization of patients' skin (with daily chlorohexidine baths), improved cleaning of environmental surfaces, identification of carriers of KPC-producing strains (with admission and surveillance cultures), isolation and contact precautions (pre-emptive contact precautions and cohorting of high-risk patients at admission and on the basis of the results of clinical or surveillance cultures), personnel education, and environmental cultures. Point prevalence surveys were also conducted.	Point prevalence of rectal carriage of KPC-producing strains and occurrence of CPE colonisations and clinical cases	Baseline point prevalence surveillance (one month before start of the intervention) showed a prevalence of colonization with KPC-producing isolates of 21% (8 of 39 patients screened). From 1st January 2008, until the intervention, 8 KPC-positive clinical cases were detected.	Prevalence of colonisations at each of the five surveys after implementation of the intervention were: 12%, 5%, 3%, 0% and 0%. From implementation of the intervention to 31st December 2008, only 2 KPC-positive clinical cases were detected	Rectal carriage of KPC-producing strains was found at a decreasing rate over the course of the intervention ($p<0.001$)

Author, publication year	Type of study	Control measures used in comparator group	Control measures used in intervention group	Outcome measure	Outcome in comparator group (e.g. CPE rate or number of cases)	Outcome in intervention group (e.g. CPE rate or number of cases)	Supporting statistics
Ben-David, 2010[39]	Quasi-experimental study	During the pre-intervention period (January 2006 through May 2007) contact precautions were implemented for the management of patients with clinical isolates of carbapenem-resistant *K. pneumoniae*. Detection of carbapenem-resistant *K. pneumoniae* was based on culture of clinical samples only.	For the intervention (June 2007 through December 2008), an enhanced national infection control program was added to the baseline protocol (May 2007), the national programme included: contact precautions for the care of all patients with carbapenem-resistant *K. pneumoniae* colonization or infection; the prevalence of colonization or infection was reported daily, and this information was mailed to the hospital management and the national coordinator; and patients infected with carbapenem-resistant *K. pneumoniae* had their names entered into a database so that they could be identified at hospital readmission. In addition to the measures taken in accordance with the national infection control program, an active surveillance program was initiated and included obtaining rectal culture samples from patients hospitalized in intensive care units and in step-down units, at admission to the unit and once weekly until the patient was discharged. In other departments, surveillance culture samples were only obtained from patients with epidemiologic links to persons from whom a carbapenem-resistant *K. pneumoniae* isolate had been recovered.	Incidence of clinical infection with carbapenem-resistant *K. pneumoniae*	Incidence was 6.93 cases per 10,000 patient-days during the last quarter of the pre-intervention period	Incidence was 1.8 cases per 10,000 patient-days during the last quarter of the intervention period	Incidence of clinical infection with carbapenem-resistant *K. pneumoniae* has decreased 4.7-fold ($p<0.001$). Linear regression was used to assess the change in the number of cases of infection per 10,000 patient-days over time, before and after the intervention. The change in slope was from 0.12 to -0.07 during the pre-intervention and intervention periods respectively ($p<0.001$).

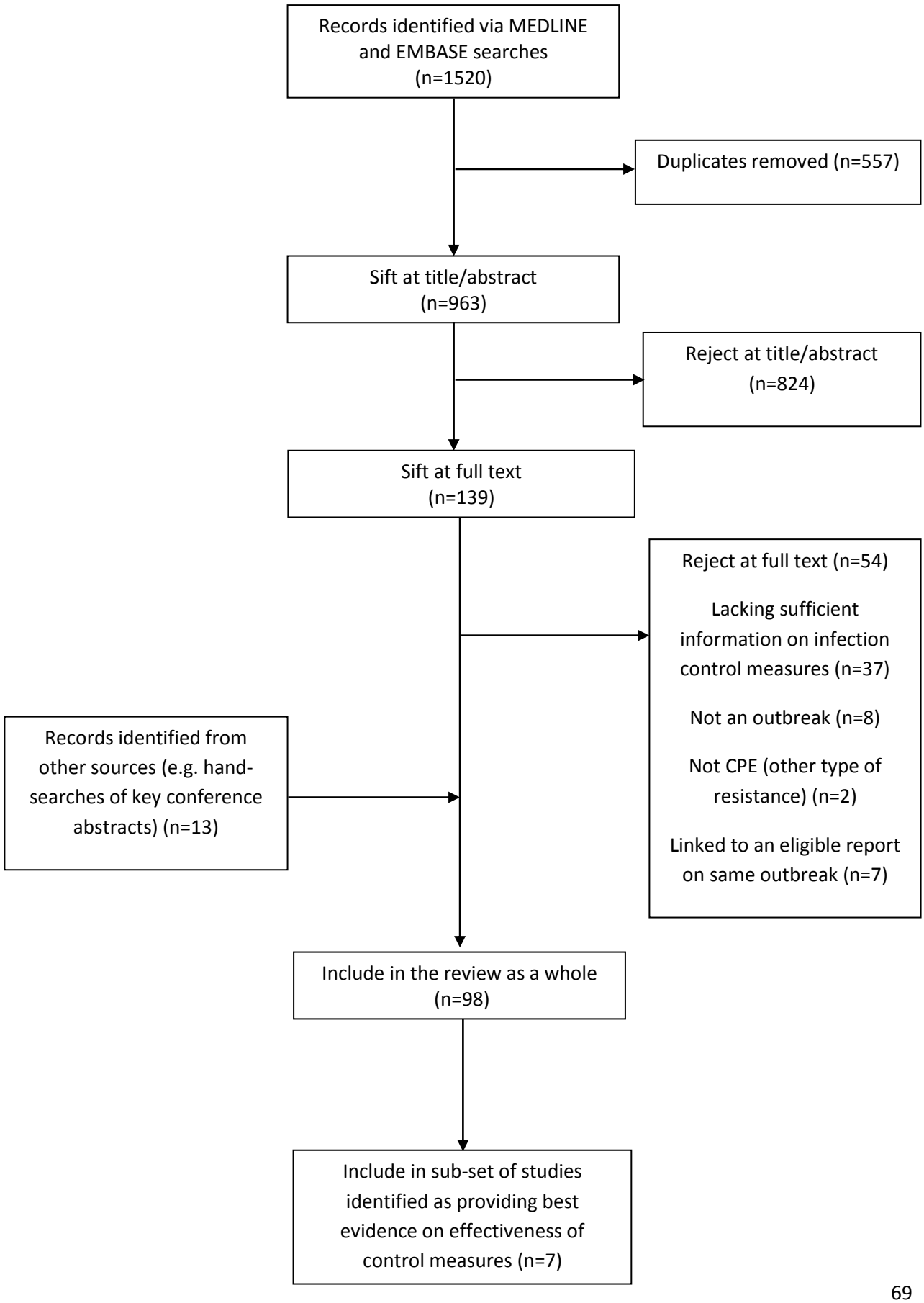
Author, publication year	Type of study	Control measures used in comparator group	Control measures used in intervention group	Outcome measure	Outcome in comparator group (e.g. CPE rate or number of cases)	Outcome in intervention group (e.g. CPE rate or number of cases)	Supporting statistics
Borer, 2011[40]	Quasi-experimental before-and-after, interrupted time-series study.	Retrospectively, all relevant data were collected from the medical records of patients with CRKP infections from May 2006 through April 2007, the pre-intervention period. Details of pre-intervention measures not specified	From May 1, 2007, through May 1, 2010, the post-intervention period, the intervention was applied and prospectively followed. The five key elements of the intervention were: 1a) an emergency department flagging system of high risk patients. 1b) On admission these flagged, high-risk patients were placed in pre-emptive isolation pending culture results and rectal cultures for CRKP performed for all patients. Strict contact precautions; signage; 1:4 ratio of trained nurses to patients and a dedicated housekeeping team. 2) CRKP-positive patients cohorted together on a separate ward or area. The building of a cohort ward (involved strict isolation; dedicated nursing staff and equipment, including an X-ray machine and monitors; visitor education; and environmental disinfection(details given)), 3) intensive active surveillance in high-risk wards (included surveillance cultures performed at admission, weekly there-after, and at discharge; CRKP-positive ICU patients placed in private rooms or the cohort ward when stable), 4) epidemiological investigations (included identification of new CRKP patients within the hospital; immediate and intensive review of case and contacts by the infection control practitioner; rectal surveillance cultures; enforcement of compliance with hand hygiene, contact precautions, and disinfection protocols), 5) new carbapenem-restriction policy	Incidence of newly diagnosed CRKP infections per 10,000 patient-days	From May 2006 through April 2007 (pre-intervention), incidence density was 5.26 per 10,000 patient-days	After the intervention, the incidence density was reduced to 2.91 in December 2007, followed by 1.91, 1.28, and 0.18 in 2008, 2009, and January-May 2010, respectively	p<0.001 comparing 5.26 with 0.18 per 10,000 patient-days. Changes in hospital-wide monthly incidence of infection: slope 12 months before intervention: p<0.002 (CI: -0.032 to 0.001); change in slope: p=0.004 (CI: -0.204, -0.040), slope 36 months after intervention: p=0.004 (CI: -0.013 -0.003)

Author, publication year	Type of study	Control measures used in comparator group	Control measures used in intervention group	Outcome measure	Outcome in comparator group (e.g. CPE rate or number of cases)	Outcome in intervention group (e.g. CPE rate or number of cases)	Supporting statistics
Chitnis, 2012[41]	Stepwise introduction of infection control measures	Stepwise introduction of the intervention with the first intervention period (starting July 2010) used as the comparator: Beginning in January 2010, all patients were presumptively placed under contact precautions upon admission and had urine and sputum surveillance cultures collected within 3 days of admission to screen for multi-drug resistant organisms (MDROs), including CRE. Patients with a history of or who tested positive for an MDRO remained under contact precautions for their entire hospitalization. Rectal screening for all patients began in July 2010 and a point-prevalence survey was conducted. As part of the on-site epidemiologic investigation conducted in March 2011, more than 40 hours of infection prevention observations of healthcare personnel (HCP) were conducted. A stepwise process of implementing infection prevention measures was initiated on the basis of results of biweekly CRE point-prevalence surveys and observations: 1) Beginning in July 2010, addition of audits of glove and gown use to ongoing weekly hand hygiene audits, monthly educational sessions on proper hand hygiene and isolation precautions for all HCP, and weekly reminders on appropriate cleaning practices for high-touch surfaces to environmental services staff.	Subsequent stages of the intervention: 2) Starting in December 2010, CRE patients were cohorted and spatially separated from non-CRE patients into one section of a medical-surgical unit with dedicated nursing staff. Daily staff meetings were conducted to increase facility communication about CRE prevention efforts. 3) In March 2011, additional recommendations from the on-site investigation were implemented, including daily audits of hand hygiene and PPE use, observations of insertion and maintenance practices for invasive devices, and daily assessments of the need for invasive devices, especially urinary catheters. Biweekly conference calls with local and state health departments, and the CDC were initiated in April 2011 to discuss results of ongoing point-prevalence surveys, to optimize infection prevention efforts at the facility, and to discuss regional CRE prevention efforts in healthcare facilities. Additional measures implemented included dedicating shared medical equipment (i.e. hover lifts, scales, and blood pressure machines) to CRE patients and assigning dedicated nursing staff to CRE patients in the intensive care unit (ICU). The facility also began a campaign to reduce unnecessary urinary catheter use concurrently with CRE-specific measures	CPE prevalence and the percentage of patients screened with newly detected CPE	CPE prevalence: 49%; percentage of patients screened with newly detected CPE: 44%	CPE prevalence: 8%; percentage of patients screened with newly detected CPE: 0%	Trends in overall CRE prevalence and proportion of screened patients with newly detected CRE were assessed using linear regression models weighted for the number of patients in the facility and the number of patients screened at the time of the bi-weekly point-prevalence surveys, respectively. The observed reduction in CPE prevalence and the percentage of patients screened with newly detected CPE were both statistically significant. Prevalence of CPE (slope = -3%/30 days; $p<0.05$); Percent of patients screened with newly detected CRE (slope = -2%/30 days; $p<0.05$)

Author, publication year	Type of study	Control measures used in comparator group	Control measures used in intervention group	Outcome measure	Outcome in comparator group (e.g. CPE rate or number of cases)	Outcome in intervention group (e.g. CPE rate or number of cases)	Supporting statistics
Ciobotaro, 2011[42]	Quasi-experimental study	Details of pre-intervention measures not specified. Pre-intervention period from January 2006 to January 2007.	The intervention (introduced February 2007) involved 3 key elements: 1) guidelines for patient isolation and cohorting, environmental cleaning, and screening (included cohorting of clinical cases and carriers; dedicated nursing personnel; strict contact precautions; detailed instructions for cleaning and disinfecting CRKP-positive patients' units were provided to all housekeeping staff; some CRKP carriers were transferred to the long-term care facility branch in an attempt to minimize the prevalence of hospitalized CRKP carriers; 2) education and training (including instruction sheets for staff, patients and caregivers; lectures; monitoring of compliance with recommendations; importance of data sharing was emphazised; hospital physicians were educated regarding the importance of restricting the use of broad-spectrum antibiotics; database on CRKP incidence and active surveillance was created), 3) automatic instructions and CRKP alerts (included immediate laboratory notification of any new CRKP isolation to both the infection control unit and the patient's ward; expanded active surveillance with computerised system for identifying high-risk patients and contacts of cases)	Incidence of carbapenem-resistant *Klebsiella pneumoniae*	No clinical cases of CRKP were recorded in the first quarter of 2006. Between May and December 2006, the CRKP incidence was 3.4/10,000 patient-days. During the first months of 2007, the incidence peaked at 8.2/10,000 patient-days.	The average incidence of clinical CRKP cases declined from 6.6/10,000 patient-days in the first 5 months of 2007 to 2.5/ 10,000 patient-days in the last 7 months of 2007. From January 2008 up to the end of the study, the average incidence was 0.5/10,000 patient-days, which was 16-fold lower than the peak incidence	Poisson segmented regression demonstrated a significant difference in slope before and after the intervention ($p<0.001$). The slope showed that during each month after the intervention, the number of CRKP cases decreased by a factor of 0.91 (95% CI: 0.85-0.97) compared with the previous month

Author, publication year	Type of study	Control measures used in comparator group	Control measures used in intervention group	Outcome measure	Outcome in comparator group (e.g. CPE rate or number of cases)	Outcome in intervention group (e.g. CPE rate or number of cases)	Supporting statistics
Cohen, 2011[43]	Consecutive intervention analyses	Details of pre-intervention measures not specified. The first stage of the intervention was used as the comparator. Intervention 1 (began March 2006): isolation for patients colonized or infected with CRKP in single rooms (where possible) and contact precautions	Intervention 2 (began March 2007): Cohorting of patients and nursing staff, screening of patients in the same room as newly identified carriers of CRKP ("snow ball" active surveillance), local protocol for continued cohorting of returning patients, and environmental cleaning of the cohort areas performed daily according to a checklist; Intervention 3 (began August 2008): Weekly active surveillance in the intensive care unit; Intervention 4 (began March 2009): Selective surveillance of patients on admission to the emergency department	CRKP incidence (total number of cases of in-hospital CRKP acquisition detected by clinical cultures - each patient was only counted once) and prevalence (included both clinical and surveillance cultures and was calculated on the basis of weekly point-prevalence studies). Both measures were reported as cases per 1,000 hospital beds	During intervention period 1: mean incidence 8.4 cases per 1,000 hospital beds (slope coefficient: 1.9), mean prevalence 10.4 cases per 1,000 (slope coefficient: 2.0)	Intervention period 2: mean incidence 13.4 cases per 1,000 hospital beds (slope coefficient: -0.7, p<0.001), mean prevalence: 20.2 (slope coefficient: -0.01, p<0.01); Intervention period 3): mean incidence 8.3 (slope coefficient: -0.8, p=0.76), mean prevalence: 17.4 (slope coefficient: -0.4, 0.77); Intervention period 4: mean incidence 4.3 (slope coefficient: -0.008, p=-0.27), mean prevalence: 13.5 (slope coefficient: -1.0, p=0.6)	The regression analyses showed that only intervention 2, the cohorting intervention, was associated with a significant change in both the incidence (p<0.001) and the prevalence rates (p<0.001).

Figure 1. Study selection flow chart



Appendix

Search 1 - Medline and Medline in-process citations, January 2000 to May 2015

1. carbapenemase/ or carbapenemase$.ti,ab,ot.
2. ((carbapenem$ or klebsiella) adj3 (produc$ or secret$ or resist$ or emit$ or generat$ or block$ or immun$ or antagoni$ or "not susceptib$" or unsusceptib$ or un-susceptib$ or non-suscepti$ or non-suscepti$)).ti,ab,ot,hw.
3. (kpc or vim or mbl or oxa or oxacillinase or oxa48 or metallo-beta-lactamase or "metallo-b-lactamase" or NDM$).ti,ab,ot.
4. or/1-3
5. enterobacteriaceae/ or exp citrobacter/ or exp enterobacter/ or exp escherichia/ or exp hafnia/ or exp klebsiella/ or exp kluyvera/ or exp morganella/ or exp proteus/ or exp providencia/ or exp serratia/
6. enterobacteriaceae infection/ or exp escherichia coli infection/ or exp klebsiella infection/ or exp proteus infection/ or exp serratia infection/
7. (enterobacter$ or entero-bacter$ or klebsiella or citro-bact$ or citrobact$ or escherichia or hafnia or morganell$ or proteus or serratia or "e coli" or "e.coli").ti,ab,ot.
8. (kluyvera or providencia or "E.aerogenes" or "e aerogenes" or "k.oxytoca" or "k oxytoca" or "k pneumonia$" or "k.pneumonia$" or "e cloacae" or "e.cloacae").ti,ab,ot.
9. or/5-8
10. 4 and 9
11. (CPE or CPEs or CRE or CREs or CNSE).ti,ab,ot.
12. 10 or 11
13. ((CP or CR) adj2 (enterobacter$ or entero-bacter$)).ti,ab,ot.
14. 12 or 13
15. (outbreak or cluster).mp.
16. 14 and 15
17. (2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).dd.
18. 16 and 17
19. (2000$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).em.
20. 16 and 19
21. 18 or 20
22. carbapenemase/ or carbapenemase$.ti,ab,ot.
23. ((carbapenem$ or klebsiella) adj3 (produc$ or secret$ or resist$ or emit$ or generat$ or block$ or immun$ or antagoni$ or "not susceptib$" or unsusceptib$ or un-susceptib$ or non-suscepti$ or non-suscepti$)).ti,ab,ot,hw.
24. (kpc or vim or mbl or oxa or oxacillinase or oxa48 or metallo-beta-lactamase or "metallo-b-lactamase" or NDM$).ti,ab,ot.
25. or/22-24
26. enterobacteriaceae/ or exp citrobacter/ or exp enterobacter/ or exp escherichia/ or exp hafnia/ or exp klebsiella/ or exp kluyvera/ or exp morganella/ or exp proteus/ or exp providencia/ or exp serratia/
27. enterobacteriaceae infection/ or exp escherichia coli infection/ or exp klebsiella infection/ or exp proteus infection/ or exp serratia infection/
28. (enterobacter$ or entero-bacter$ or klebsiella or citro-bact$ or citrobact$ or escherichia or hafnia or morganell$ or proteus or serratia or "e coli" or "e.coli").ti,ab,ot.
29. (kluyvera or providencia or "E.aerogenes" or "e aerogenes" or "k.oxytoca" or "k oxytoca" or "k pneumonia$" or "k.pneumonia$" or "e cloacae" or "e.cloacae").ti,ab,ot.
30. or/26-29

31. 25 and 30
32. (CPE or CPEs or CRE or CREs or CNSE).ti,ab,ot.
33. 31 or 32
34. ((CP or CR) adj2 (enterobacter$ or entero-bacter$)).ti,ab,ot.
35. 33 or 34
36. (outbreak or cluster).mp.
37. (200$ or 201$).ed,dc. or (200$ or 201$).yr.
38. 35 and 36 and 37

Search 2 – Embase, January 2000 to May 2015

1. carbapenemase/ or carbapenemase$.ti,ab,ot.
2. ((carbapenem$ or klebsiella) adj3 (produc$ or secret$ or resist$ or emit$ or generat$ or block$ or immun$ or antagoni$ or "not susceptib$" or unsusceptib$ or un-susceptib$ or non-suscepti$ or non-suscepti$)).ti,ab,ot,hw.
3. (kpc or vim or mbl or oxa or oxacillinase or oxa48 or metallo-beta-lactamase or "metallo-b-lactamase" or NDM$).ti,ab,ot.
4. or/1-3
5. enterobacteriaceae/ or exp citrobacter/ or exp enterobacter/ or exp escherichia/ or exp hafnia/ or exp klebsiella/ or exp kluyvera/ or exp morganella/ or exp proteus/ or exp providencia/ or exp serratia/
6. enterobacteriaceae infection/ or exp escherichia coli infection/ or exp klebsiella infection/ or exp proteus infection/ or exp serratia infection/
7. (enterobacter$ or entero-bacter$ or klebsiella or citro-bact$ or citrobact$ or escherichia or hafnia or morganell$ or proteus or serratia or "e coli" or "e.coli").ti,ab,ot.
8. (kluyvera or providencia or "E.aerogenes" or "e aerogenes" or "k.oxytoca" or "k oxytoca" or "k pneumonia$" or "k.pneumonia$" or "e cloacae" or "e.cloacae").ti,ab,ot.
9. or/5-8
10. 4 and 9
11. (CPE or CPEs or CRE or CREs or CNSE).ti,ab,ot.
12. 10 or 11
13. ((CP or CR) adj2 (enterobacter$ or entero-bacter$)).ti,ab,ot.
14. 12 or 13
15. (200$ or 201$).dd.
16. 14 and 15
17. (200$ or 201$).em.
18. 14 and 17
19. 16 or 18
20. (outbreak or cluster).mp.
21. 19 and 20